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SLOVENIAN ASSOCIATION OF GASTROENTEROLOGY AND HEPATOLOGY
SLOVENSKO ZDRUŽENJE ZA GASTROENTEROLOGIJO IN HEPATOLOGIJO



Gastroenterologija je eno izmed področij medicine, na katerih se nova spoznanja posebej hitro prepletajo z vsakodnevno klinično prakso. Bolezni prebavil, jeter in trebušne slinavke vse pogostejše obravnavamo v tesnem sodelovanju z abdominalnimi kirurgi, onkologi, radiologi in drugimi specialisti. Prav interdisciplinarnost in usmerjenost k posameznemu bolniku povezujeta prispevke tokratne številke naše revije.

Pomemben del sodobne obravnave bolezni jeter predstavljajo minimalno invazivni kirurški posegi. Raziskava o laparoskopski resekciji benignih jetrnih tumorjev prikazuje izkušnje terciarnega centra in opozarja, da lahko poseg pri skrbno izbranih simptomatskih bolnikih pomembno izboljša kakovost življenja. Izboljšanje simptomov po operaciji so ugotovili pri približno dveh tretjinah simptomatskih bolnikov. Ob tem velja poudariti, da večina benignih jetrnih sprememb kirurškega zdravljenja ne potrebuje; ključna je zato pravilna indikacija.

Izvirna raziskava o akutnem pankreatitisu v času pandemije covida-19 osvetljuje, kako lahko izredne zdravstvene razmere vplivajo na značilnosti obravnavanih bolnikov. V pandemičnem obdobju so avtorji ugotovili večji delež biliarnega pankreatitisa in višje vrednosti pankreatičnih encimov, ne pa pomembnih razlik v bolnišnični umrljivosti ali trajanju hospitalizacije. Z neugodnim izidom so bili pomembno povezani predvsem zapleti. Ugotovitve so dragocene tudi za razmislek o organizaciji oskrbe ob prihodnjih zdravstvenih krizah.

V ospredje raziskovalnega zanimanja vse izraziteje stopa črevesna mikrobiota. Pregledni prispevek o njeni vlogi pri nastanku in zdravljenju raka debelega črevesa in danke prikazuje zapletene povezave med mikroorganizmi, imunskim odzivom in tumorskim mikrokoljem. Opozarja tudi, da lahko kirurško in multimodalno onkološko zdravljenje spreminjata sestavo mikrobiote, kar bi lahko vplivalo na zaplete in dolgoročne izide. Čeprav se odpirajo nove mož-

nosti preprečevanja in zdravljenja, je treba njihovo klinično uporabnost še natančneje opredeliti.

Sodobne možnosti zdravljenja peritonealnih metastaz obravnava prispevek o citoreduktivni kirurgiji in hipertermični intraperitonealni kemoterapiji. Pri ustrezno izbranih bolnikih je mogoče doseči dolgotrajno preživetje, vendar koristi niso enake pri vseh vrstah malignomov. Za uspeh so odločilni obseg bolezni, možnost popolne citoredukcije in izkušnost multidisciplinarnega tima. Zahtevnost postopkov zato poudarja pomen obravnave v specializiranih centrih.

Interdisciplinarno razsežnost gastroenterologije nazorno ponazarja tudi pregled gastrointestinalnih, presnovnih in prehranskih zapletov po urinarnih črevesnih preusmeritvah. Kronična presnovna acidoza, malabsorpcija, driska, prehranska pomanjkanja in bakterijska razrast lahko bolnike spremljajo še dolgo po operaciji. Pravočasno prepoznavanje teh težav zahteva strukturirano dolgoročno spremljanje ter sodelovanje urologov, abdominalnih kirurgov, gastroenterologov in drugih strokovnjakov.

Varnost zdravljenja se ne konča pri predpisanih zdravilih. Prispevek o nutrivigilanci in primeru akutne jetrne okvare ob uporabi pripravka z indijsko melijo nas opominja, da tudi prehranska dopolnila rastlinskega izvora niso nujno neškodljiva. Pri nepojasnjeni jetrni okvari je zato pomembno sistematično povprašati po prehranskih dopolnilih in pripravkih za samozdravljenje ter poročati o domnevnih neželenih učinkih.

Pomembno diagnostično vprašanje odpira pregled neposrednih bioloških označevalcev uživanja alkohola. Etanol v krvi omogoča ugotavljanje zelo nedavne izpostavljenosti, etilglukuronid (EtG) je uporaben za spremljanje nedavnega uživanja, fosfatidiletanol (PEth) pa omogoča vpogled v daljše časovno obdobje. Označevalci se zato dopolnjujejo; njihova pravilna interpretacija je posebej pomembna pri obravnavi

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bolezni jeter, zdravljenju motnje zaradi uživanja alkohola in pri presoji pred presaditvijo jeter.

Klinični primer sindroma utesnitve sprednjega kožnega živca trebušne stene (ACNES) pa nas vrača k temeljem klinične medicine. Kronična bolečina v trebuhu ne izvira vedno iz notranjih organov. Skrbna anamneza, usmerjen klinični pregled in širše diferencialno-diagnostično razmišljanje lahko preprečijo nepotrebne preiskave ter omogočijo pravočasno in ustrezno zdravljenje.

Prispevki tokratne številke kažejo širino gastroenterologije – od kirurških inovacij in onkološkega zdravljenja do mikrobiote, presnovnih zapletov, varnosti prehranskih dopolnil in diagnostičnih dilem. Povezuje jih spoznanje, da kakovostna medicina ne temelji le na novih tehnologijah, temveč tudi na kritični presoji, sodelovanju različnih strok in pozornosti do bolnika. Vsem avtorjem se zahvaljujem za njihove prispevke, bralcem pa želim prijetno in strokovno spodbudno branje.

Prof. dr. Borut Štabuc, dr. med.
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Does laparoscopic liver resection relieve symptoms in patients with benign liver tumors?

Ali laparoskopska resekcija jeter ublaži simptome pri bolnikih z benignimi tumorji jeter?

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Keywords: laparoscopy; liver resection; symptom relief; hemangioma; focal nodular hyperplasia; hepatocellular adenoma.

Ključne besede: laparoskopija; resekcija jeter; zmanjšanje simptomov; hemangiom; fokalna nodularna hiperplazija; hepatocelularni adenom.

ABSTRACT

Background: Modern imaging increasingly detects benign liver tumours. Most are managed conservatively, but surgery may be indicated for symptoms, tumour growth, diagnostic uncertainty, or tumour-related risk.

Aim: To evaluate symptom relief and perioperative outcomes after laparoscopic liver resection for benign liver tumours in a single-centre cohort.

Materials and Methods: We retrospectively analysed patients who underwent laparoscopic liver resection for benign lesions at University Medical Centre Maribor between April 2008 and August 2025. We included the patients with histologically confirmed hemangioma, hepatocellular adenoma, or focal

IZVLEČEK

Izhodišče: Benigne tumorje jeter zaradi sodobnih slikovnih preiskav odkrivamo vse pogosteje. Večino zdravimo konzervativno, pri izbranih bolnikih pa je resekcija indicirana zaradi simptomov, rasti tumorja, diagnostične negotovosti ali tveganj, povezanih s tumorjem.

Namen: Oceniti zmanjšanje simptomov ter perioperativne izide po laparoskopski resekciji jeter zaradi benignih tumorjev.

Materiali in metode: Retrospektivno smo analizirali bolnike, pri katerih je bila med aprilom 2008 in avgustom 2025 v Univerzitetnem kliničnem centru Maribor opravljena laparoskopska resekcija jeter zaradi benignih tumorjev. Vključeni so bili bolniki s

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nodular hyperplasia. We collected preoperative, perioperative, postoperative, and follow-up data. We assessed symptom relief 12 months after surgery.

Results: We included 19 patients: five with hepatocellular adenoma, eight with hemangioma, and six with focal nodular hyperplasia. The main indication was symptoms in 12 patients (63.2%), followed by diagnostic uncertainty in four (21.1%) and tumour growth in three (15.8%). Median tumour diameter was 5.5 cm, operative time was 120 minutes, blood loss was 20 mL, and hospital stay was 4 days. No intraoperative complications occurred. One postoperative complication with Clavien-Dindo grade I was recorded (5.3%). Symptoms improved in 8 of the 12 symptomatic patients (66.7%), indicating a statistically significant postoperative improvement ($p = 0.008$).

Conclusions: Laparoscopic liver resection was safe and provided symptom relief in most symptomatic patients with benign liver tumours.

histološko potrjenim hemangiomom, hepatocelularnim adenomom ali fokalno nodularno hiperplazijo. Zbrali smo perioperativne podatke in podatke kontrolnih pregledov. Zmanjšanje simptomov smo ocenili 12 mesecev po operaciji.

Rezultati: Vključenih je bilo 19 bolnikov: pet s hepatocelularnim adenomom, osem s hemangiomom in šest s fokalno nodularno hiperplazijo. Najpogostejša indikacija za resekcijo so bili simptomi pri 12 bolnikih (63,2 %), sledili sta diagnostična negotovost pri štirih (21,1 %) in rast tumorja pri treh (15,8 %). Mediana premera tumorja je bila 5,5 cm, trajanja operacije 120 minut, izgube krvi 20 mL in hospitalizacije 4 dni. Intraoperativnih zapletov, preklapov v odprto metodo, poškodb okolnih struktur, transfuzij ali smrtnosti ni bilo. Zabeležen je bil en pooperacijski zaplet stopnje I po klasifikaciji Clavien-Dindo (5,3 %). Zmanjšanje simptomov je bilo doseženo pri 8 od 12 simptomatskih bolnikov (66,7 %) in je bilo statistično značilno ($p = 0,008$).

Zaključki: Laparoskopska resekcija jeter je varna metoda in pri dveh tretjinah simptomatskih bolnikov z benignimi tumorji jeter prispeva k ublažitvi simptomov.

INTRODUCTION

Benign liver tumours are increasingly detected because of the widespread use and improved quality of modern imaging. Hemangioma, focal nodular hyperplasia (FNH), and hepatocellular adenoma (HCA) represent the most common benign solid liver lesions (1, 2). Many of these lesions are discovered incidentally during abdominal imaging performed for unrelated reasons, particularly in middle-aged women (3, 4). Hemangiomas are reported 2–6 times more frequently, FNH eight times more frequently, and HCA up to ten times more frequently in women than in men (5).

Advances in diagnostic imaging, particularly magnetic resonance imaging with hepatobiliary contrast

agents, have improved the characterisation of benign liver lesions. Nevertheless, reliable differentiation between HCA, FNH, and well-differentiated hepatocellular carcinoma can still be difficult in selected cases. When malignancy cannot be confidently excluded, diagnostic uncertainty may therefore become an indication for surgical resection (2, 3).

Although most benign liver tumours remain asymptomatic, some patients report abdominal pain, pressure, discomfort, or fullness, especially when lesions are large or located close to surrounding structures (6).

The management of benign liver tumours remains individualized. It depends on tumour type, size, growth pattern, symptoms, and the risk of complications (3, 4, 7) FNH and haemangiomas usually carry

no significant risk of malignant transformation. They are therefore managed conservatively in most cases. In contrast, HCA, particularly those larger than 5 cm, may be associated with haemorrhage or malignant transformation, and resection is commonly recommended when these risks are clinically relevant. For patients with smaller lesions or lesions without clear malignant potential, the indication for surgery is less well defined. Symptoms and their effect on quality of life often influence the decision (4, 6, 8).

A major challenge in clinical decision-making is determining whether non-specific abdominal symptoms are truly attributable to the liver lesion. This uncertainty must be balanced against the risks of surgery, even though liver resection is considered safe in experienced centres and is associated with low mortality and acceptable morbidity (2–4). The role of resection for benign disease still requires careful patient selection.

This study aimed to evaluate perioperative and postoperative outcomes after laparoscopic liver resection for benign liver tumours, with particular focus on symptom relief.

Materials and Methods

We retrospectively maintained database of patients who underwent liver resection at University Medical Centre Maribor between April 2008 and August 2025. Patients were eligible for inclusion if they underwent laparoscopic liver resection for a benign liver lesion, namely liver haemangioma, HCA, or FNH, confirmed by the final histopathological diagnosis.

At the time of surgery, all patients consented to the use of anonymised data for research purposes. Medical records were anonymised before analysis. Because of the retrospective design, the local Ethics Committee waived the requirement for formal approval.

For each eligible patient we extracted, demographic, perioperative, and follow-up data from the database. We analysed the data for the entire cohort and

separately by final histopathological diagnosis: HCA, haemangioma, or FNH.

Preoperative variables included sex, age, body mass index, American Society of Anaesthesiologists (ASA) score, liver steatosis, tumour diameter, Southampton difficulty score (9), and Iwate score (10). The indication for surgery was classified as diagnostic uncertainty, tumour growth, or symptoms. Perioperative variables included the type and extent of liver resection. We first classified resections as anatomical or non-anatomical based on whether they followed segmental liver anatomy (11).

The non-anatomical resections were recorded as atypical resections. We defined anatomically major resections as resections of three or more adjacent liver segments, whereas minor resections included segmentectomies and sectionectomies involving fewer than three adjacent segments (11). Technically major resections were analysed separately and referred to resections that are anatomically minor but technically demanding because they involve posterosuperior liver segments 1, 4a, 7, or 8, which are difficult to access laparoscopically (12, 13).

Intraoperative complications were defined according to Halls et al. and included blood loss exceeding 775 mL, unintentional injury to surrounding structures, or conversion to an open approach (9). Other variables were operative time, blood loss, use and duration of hepatic pedicle clamping, and blood transfusion requirement.

Postoperative and follow-up outcomes included postoperative morbidity, mortality, length of hospital stay, and self-reported symptom relief after surgery. Postoperative morbidity was defined as any postoperative complication and was classified according to the Clavien-Dindo classification (14).

Symptom relief was assessed in patients who were symptomatic before surgery and was defined as a decrease or absence of the presenting symptoms at 12-month follow-up after laparoscopic liver resection.

Statistical analysis

We performed statistical analysis using IBM SPSS Statistics for Windows, version 31.0.0.0 (IBM Corporation, Armonk, NY, USA). We reported percentages to one decimal place, and a considered p -values < 0.05 statistically significant. We presented categorical variables as counts and percentages, and tested differences between them using the Fisher–Freeman–Halton test. We express continuous variables as medians with interquartile ran-

ges and analysed them using the Kruskal–Wallis test because the distributions were non-normal. We analysed symptom relief using McNemar’s test for paired categorical data.

Results

During the study period, 19 patients underwent laparoscopic liver resection for benign liver tumours. Final histopathology confirmed HCA in 5 patients, haemangioma in 8, and FNH in 6. Table 1 summa-

Table 1. Preoperative characteristics of 19 patients undergoing laparoscopic liver resection for benign liver tumours.

	Total (n = 19)	HCA (n = 5)	Hemangioma (n = 8)	FNH (n = 6)	p -value
Male sex ^a	6 (31.6%)	0 (0.0%)	3 (37.5%)	3 (50.0%)	0.221
Age (years) ^b	48.0 (IQR 29.0)	48.0 (IQR 39.0)	57.0 (IQR 24.0)	39.5 (IQR 17.0)	0.074
Body mass index (kg/m ²) ^b	26.2 (IQR 6.1)	26.4 (IQR 9.4)	25.3 (IQR 5.8)	28.65 (IQR 6.1)	0.728
Tumour diameter (cm) ^b	5.5 (IQR 5.5)	5.2 (IQR 4.4)	6.15 (IQR 6.5)	5.0 (IQR 8.7)	0.810
ASA score 3 ^a	2 (10.5%)	1 (20.0%)	1 (12.5%)	0 (0.0%)	0.719
Liver steatosis ^a	4 (21.1%)	1 (20.0%)	1 (12.5%)	2 (33.3%)	0.780
Median Southampton difficulty score ^b	3 (IQR 1)	3 (IQR 3)	3 (IQR 2)	3 (IQR 2)	0.823
Median Iwate score ^b	5 (IQR 1)	4 (IQR 2)	4.5 (IQR 2)	5 (IQR 1)	0.128

^a Categorical variable, Fisher–Freeman–Halton test; ^b continuous variable, Kruskal–Wallis test. ASA, American Society of Anaesthesiologists; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; IQR, interquartile range.

Table 2

	Total (n = 19)	HCA (n = 5)	Hemangioma (n = 8)	FNH (n = 6)	p -value
Diagnostic uncertainty	4 (21.1%)	2 (40.0%)	1 (12.5%)	1 (16.7%)	0.253 ^a
Tumour growth	3 (15.8%)	1 (20.0%)	0 (0.0%)	2 (33.3%)	
Symptoms	12 (63.2%)	2 (40.0%)	7 (87.5%)	3 (50%)	

^a Categorical variable, Fisher–Freeman–Halton test. FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma.

izes baseline characteristics. The median age was 48.0 years; 6 patients (31.6%) were male; the median body mass index was 26.2 kg/m²; and the median tumour diameter was 5.5 cm. No statistically significant differences were observed between histopathological groups in sex, age, body mass index, tumour diameter, ASA score, liver steatosis, Southampton difficulty score, or I wate score.

Table 2 presents indications for surgery. Symptoms were the most common indication, present in 12 patients (63.2%). Diagnostic uncertainty was the indication in 4 patients (21.1%), whereas tumour growth was noted in 3 patients (15.8%). The distribution of surgical indications did not differ significantly between patients with HCA, haemangioma, and FNH.

Table 3 shows intraoperative and postoperative outcomes.

Five patients had atypical liver resections. There were 14 anatomical resections: two patients (10.5%) underwent technically major resections (right posterior sectionectomies), seven underwent left lateral sectionectomies, and five underwent segmentectomies. There were no anatomically major resections.

Median blood loss was 20 mL, and median operative time was 120 minutes. Hepatic pedicle clamping was used in 5 patients (26.3%), with a median total clamping duration of 25 minutes among those who underwent clamping.

No intraoperative complications and no transfusion requirements were recorded. Postoperative morbidity was low, with one Clavien-Dindo grade I complication (5.3%), and no postoperative mortality occurred. The median length of hospital stay was 4 days. Among the 12 patients who were symptomatic before surgery, symptom relief was achieved in

Table 3. Intraoperative and postoperative outcomes

	Total (n = 19)	HCA (n = 5)	Haemangioma (n = 8)	FNH (n = 6)	p-value
Technically major resection ^a	2 (10.5%)	0 (0%)	1 (12.5%)	1 (16.7%)	1.000
Anatomical resections ^a	14 (73.7%)	3 (60.0%)	5 (62.5%)	6 (100.0%)	0.101
Blood loss (mL) ^b	20 (IQR 200)	60 (IQR 310)	20 (IQR 70)	115 (IQR 255)	0.775
Operative time (min) ^b	120 (IQR 50)	130 (IQR 143)	115 (IQR 31)	127.5 (IQR 46)	0.624
Hepatic pedicle clamping ^a	5 (26.3%)	2 (40.0%)	1 (12.5%)	2 (33.3%)	0.530
Total hepatic pedicle clamping duration (min) ^b	25 (IQR 19)	25 (IQR 0)	47 (IQR /)	33 (IQR /)	0.223
Intraoperative complications	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	/
Length of hospital stay (days) ^b	4 (IQR 2)	5 (IQR 1)	4.5 (IQR 3)	3.5 (IQR 1)	0.092
Postoperative complication ^a	1 (5.3%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	0.263
Symptom relief ^c	8 (66.7%)	1 (50.0%)	5 (71.4%)	2 (66.7%)	0.008

^a Categorical variable, Fisher–Freeman–Halton test; ^b continuous variable, Kruskal–Wallis test; ^c paired categorical data, McNemar’s test. FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; IQR, interquartile range.

eight patients (66.7%) at 12-month follow-up, representing a statistically significant postoperative improvement ($p = 0.008$).

Discussion

This single-centre experience suggests that laparoscopic liver resection can provide symptom relief for selected patients with benign liver tumours while maintaining a favourable perioperative safety profile. In our cohort, symptoms were the most common indication for surgery, accounting for 12 of 19 resections (63.2%) (Table 2). At 12-month follow-up, 8 of these 12 symptomatic patients achieved symptom relief (66.7%), representing a statistically significant postoperative improvement ($p = 0.008$) (Table 3). These findings support the role of surgery in carefully selected symptomatic patients, provided that other potential causes of abdominal complaints are reasonably excluded before resection, as symptom attribution in benign liver lesions is often challenging (6, 15).

Our results are broadly consistent with previous reports on liver resection for symptomatic benign liver lesions. Hoffmann et al. reported complete or partial symptom relief in 87% of symptomatic patients after resection, with no postoperative mortality and acceptable morbidity (3). Similarly, van Rosmalen et al. observed sustained symptom relief in 30 of 40 patients after a median follow-up of 54 months. However, they emphasized that establishing a causal relationship between benign liver tumours and abdominal symptoms can be difficult (6). In a systematic review including 42 studies and 4061 patients undergoing surgery for solid benign liver tumours, van Rosmalen et al. reported symptom relief in 82% of symptomatic patients after a weighted mean follow-up of 28.5 months, while noting the limited use of validated quality-of-life tools (16).

Diagnosis and management of benign liver tumours remain challenging due to varying tumor subtypes and associated risks (1). While guidelines of the

European Society for the Study of the Liver offer a helpful framework, they may not capture the full complexity of clinical practice (1). Haring et al. conducted a European study. They found variation in practice regarding lifestyle modification and imaging follow-up for patients with FNH, as well as in managing HCA larger than 5 cm before and during pregnancy (1). Additionally, management of HCA larger than 5 cm after lifestyle modification often differed from the European Society for the Study of the Liver guidelines (1).

Therefore, patient selection remains the main clinical challenge. Symptoms such as abdominal pain, pressure, discomfort, or fullness are non-specific and may persist after surgery if they are unrelated to the liver lesion. The decision to operate should be based on careful multidisciplinary assessment, including tumour type, size, location, growth pattern, diagnostic certainty, risk of complications, and the severity and persistence of symptoms (6, 7). In symptomatic patients, surgery should be considered only after alternative causes of symptoms have been excluded and after patients have been informed that symptom relief is likely but not guaranteed (7).

However, indications for surgery in benign liver tumours should remain restrictive. In our study, symptoms were the most frequent indication, followed by diagnostic uncertainty and tumour growth (Table 2). This distribution reflects current clinical practice: HCA is often resected due to the risk of haemorrhage or malignant transformation, particularly in larger lesions, whereas FNH and haemangiomas are usually managed conservatively unless symptoms, growth, or diagnostic uncertainty warrant intervention (4, 7, 17). The diagnostic evaluation of HCA and FNH relies primarily on magnetic resonance imaging and computed tomography (4). Diagnostic uncertainty was an indication for 21.1% of resections in our cohort (Table 2). It underlines that, despite advances in modern imaging, histological confirmation may still be required when malignancy cannot be confidently excluded (18).

The perioperative outcomes in this cohort support the safety of laparoscopic liver resection for benign disease in appropriately selected patients (Table 3). No intraoperative complications were recorded. Postoperative morbidity was low, with one Clavien-Dindo grade I complication (5.3%), and no postoperative mortality occurred. Median blood loss was 20 mL, median operative time was 120 minutes, and median length of hospital stay was 4 days (Table 3). These findings compare favourably with published series in which liver resection for benign disease has been associated with low mortality, acceptable morbidity, shorter recovery, and improved quality of life in selected patients (2, 3).

We performed anatomical resections in 14 patients (73.7%), with no statistically significant difference between histopathological groups (Table 3). Other perioperative outcomes, including operative time, blood loss, hepatic pedicle clamping, postoperative morbidity, and length of hospital stay, also did not differ significantly between histopathological groups.

This study has several limitations. First, the retrospective observational design limits the ability to establish a direct causal relationship between benign liver tumours and preoperative symptoms, because causal inference from observational data is vulnerable to bias and confounding (19, 20).

Second, the cohort was small and included three tumour entities, limiting subgroup analysis, reducing statistical power, and increasing the risk of imprecise estimates. Third, symptom relief was assessed clinically rather than with a validated quality-of-life or pain questionnaire; this is important because patient-reported outcome measures are increasingly recommended to capture pain, fatigue, anxiety, daily-life limitations, and quality of life in patients with benign liver tumours and cysts (15). Finally, this was a single-centre experience, and the results may not be generalisable to centres with different patient populations and surgical volumes.

Future prospective studies should employ standardised instruments to assess symptoms and quality of life, enabling a more consistent identification of patients who benefit from surgery for benign liver disease, as patient-reported outcome measures for benign liver tumours are still insufficiently standardized (15).

In conclusion, laparoscopic liver resection for benign liver tumours was safe in this cohort and was associated with significant symptom relief in most symptomatic patients. These findings support laparoscopic resection as a valuable treatment option for carefully selected patients, particularly when symptoms are persistent, diagnostic uncertainty remains, or tumour-related risks justify surgery.

References:

1. Haring MPD, de Haas RJ, van Vilsteren FGI, et al. Variation in the management of benign liver tumors: A European survey and case vignette study. *Clin Res Hepatol Gastroenterol* 2023;47(3):102094. doi: 10.1016/j.clinre.2023.102094 [published Online First: 20230211]
2. Kamphues C, Engel S, Denecke T, et al. Safety of liver resection and effect on quality of life in patients with benign hepatic disease: single center experience. *BMC Surg* 2011;11:16. doi: 10.1186/1471-2482-11-16 [published Online First: 20110726]
3. Hoffmann K, Unsinn M, Hinz U, et al. Outcome after a liver resection of benign lesions. *HPB (Oxford)* 2015;17(11):994–1000. doi: 10.1111/hpb.12496 [published Online First: 20150903]
4. Bieze M, Busch OR, Tanis PJ, et al. Outcomes of liver resection in hepatocellular adenoma and focal nodular hyperplasia. *HPB (Oxford)* 2014;16(2):140–9. doi: 10.1111/hpb.12087 [published Online First: 20130319]
5. Trotošek B, Djokić M, Petrič M, et al. Priporočila za obravnavo benignih jetrnih tumorjev = Recommendations for management of benign liver tumors. *Gastroenterolog* 2018;22(1):20-29.
6. van Rosmalen BV, Bieze M, Besselink MG, et al. Long-term outcomes of resection in patients with symptomatic benign liver tumours. *HPB (Oxford)* 2016;18(11):908–14. doi: 10.1016/j.hpb.2016.07.013 [published Online First: 20160821]
7. EASL Clinical Practice Guidelines on the management of benign liver tumours. *J Hepatol* 2016;65(2):386–98. doi: 10.1016/j.jhep.2016.04.001 [published Online First: 20160413]
8. Nault JC, Paradis V, Ronot M, et al. Benign liver tumours: understanding molecular physiology to adapt clinical management. *Nat Rev Gastroenterol Hepatol* 2022;19(11):703–16. doi: 10.1038/s41575022-00643-5 [published Online First: 20220714]
9. Halls MC, Berardi G, Cipriani F, et al. Development and validation of a difficulty score to predict intraoperative complications during laparoscopic liver resection. *Br J Surg* 2018;105(9):1182–91. doi: 10.1002/bjs.10821 [published Online First: 20180508]
10. Wakabayashi G. What has changed after the Morioka consensus conference 2014 on laparoscopic liver resection? *Hepatobiliary Surg Nutr* 2016;5(4):281–9. doi: 10.21037/hbsn.2016.03.03 [published Online First: 2016/08/09]

11. Strasberg SM, Belghiti J, Clavien PA, et al. The Brisbane 2000 Terminology of Liver Anatomy and Resections. *HPB* 2000;2(3):333–39. doi: 10.1016/s1365-182x(17)30755-4
12. Kazaryan AM, Rosok BI, Marangos IP, et al. Comparative evaluation of laparoscopic liver resection for posterosuperior and anterolateral segments. *Surg Endosc* 2011;25(12):3881–9. doi: 10.1007/s00464-011-1815-x [published Online First: 20110707]
13. Abu Hilal M, Aldrighetti L, Dagher I, et al. The Southampton Consensus Guidelines for Laparoscopic Liver Surgery: From Indication to Implementation. *Ann Surg* 2018;268(1):11–18. doi: 10.1097/SLA.0000000000002524 [published Online First: 2017/10/25]
14. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250(2):187–96. doi: 10.1097/SLA.0b013e3181b13ca2 [published Online First: 2009/07/30]
15. Furumaya A, Nooijen LE, Haring MPD, et al. Development of a set of patient reported outcome measures for patients with benign liver tumours and cysts: patient focus groups and systematic review. *J Patient Rep Outcomes* 2022;6(1):124. doi: 10.1186/s41687-022-00531-1 [published Online First: 20221209]
16. van Rosmalen BV, de Graeff JJ, van der Poel MJ, et al. Impact of open and minimally invasive resection of symptomatic solid benign liver tumours on symptoms and quality of life: a systematic review. *HPB (Oxford)* 2019;21(9):1119–30. doi: 10.1016/j.hpb.2019.02.022 [published Online First: 20190327]
17. Herman P, Fonseca GM, Kruger JAP, et al. Laparoscopic liver resection for benign tumors: the current position. *Arq Bras Cir Dig* 2022;34(4):e1641. doi: 10.1590/0102-672020210002e1641 [published Online First: 20220131]
18. Hau HM, Kloss A, Wiltberger G, et al. The challenge of liver resection in benign solid liver tumors in modern times - in which cases should surgery be done? *Z Gastroenterol* 2017;55(7):639–52. doi: 10.1055/s-0043-110145 [published Online First: 20170714]
19. Wang MT, Bolland MJ, Grey A. Reporting of Limitations of Observational Research. *JAMA Intern Med* 2015;175(9):1571–2. doi: 10.1001/jamainternmed.2015.2147
20. Dahabreh IJ, Bibbins-Domingo K. Causal Inference About the Effects of Interventions From Observational Studies in Medical Journals. *Jama* 2024;331(21):1845–53. doi: 10.1001/jama.2024.7



Acute Pancreatitis During the SARS-CoV-2 Pandemic: From aetiology to outcome

Akutni pankreatitis med SARS-CoV 2 pandemijo: od etiologije do izida

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Keywords: acute pancreatitis, aetiology, COVID-19 pandemic, complications, mortality

Ključne besede: akutni pankreatitis, etiologija, COVID-19 pandemija, zapleti, smrtnost

ABSTRACT

Background: The COVID-19 pandemic disrupted healthcare systems and delayed access to medical care. Its impact on the aetiology, clinical course, and outcomes of acute pancreatitis remains unclear.

Aim: To evaluate the impact of the COVID-19 pandemic on the ethology, clinical course, complications, and mortality of patients with acute pancreatitis in a tertiary care centre.

Materials and Methods: We conducted a retrospective cohort study including 418 patients with clinically, biochemically, and radiologically confirmed acute pancreatitis treated between January 2020 and December 2024. We stratified the patients into pandemic and non-pandemic periods. We assessed disease severity using the modified Balthazar index. We used chi-square tests and logistic regression for statistical analyses.

IZVLEČEK

Izhodišče: Pandemija COVID-19 je pomembno vplivala na delovanje zdravstvenih sistemov in dostopnost zdravstvene oskrbe. Njen vpliv na etiologijo, klinični potek in izide akutnega pankreatitisa še ni povsem pojasnjen.

Namen: Oceniti vpliv pandemije COVID-19 na etiologijo, klinični potek, zaplete in umrljivost bolnikov z akutnim pankreatitisom v terciarnem centru.

Material in metode: Izvedli smo retrospektivno kohortno raziskavo, v katero smo vključili 418 bolnikov s klinično, laboratorijsko in slikovno potrjenim akutnim pankreatitisom, zdravljenih med januarjem 2020 in decembrom 2024. Bolnike smo razdelili glede na obdobje obravnave (med pandemijo in izven nje). Stopnjo bolezni smo ocenili z modificiranim Balthazarjevim indeksom. Uporabili smo hi-kvadrat test in logistično regresijo.

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Results: Of 418 patients, 46.7% were treated during the pandemic. Aetiology differed significantly ($p = 0.028$), with a higher proportion of biliary pancreatitis during the pandemic (45.6% vs 31.8%). Lipase levels were significantly higher during the pandemic ($p < 0.001$), while C-reactive protein levels and length of hospital stay did not differ significantly. Walled-off necrosis occurred in 6.5% of patients and was associated with prolonged hospitalisation (mean 25 ± 20 days, $p < 0.001$). Overall, in-hospital mortality was 3.3% and was strongly associated with the number of complications ($p < 0.001$).

Conclusions: The pandemic was associated with a shift toward biliary aetiology and higher enzyme levels, likely reflecting delayed presentation. However, mortality and length of hospital stay did not change. The number of complications was the main predictor of in-hospital mortality.

Rezultati: Med 418 bolniki jih je bilo 46,7 % obravnavanih med pandemijo. Etiološka porazdelitev se je značilno razlikovala ($p = 0,028$), pri čemer je bil med pandemijo večji delež biliarnega pankreatitisa (45,6 % proti 31,8 %). Vrednosti lipaze so bile med pandemijo značilno višje ($p < 0,001$), medtem ko vrednosti C-reaktivnega proteina in dolžina hospitalizacije niso pokazale značilnih razlik. Omejena nekroza je bila prisotna pri 6,5 % bolnikov in je bila povezana z daljšo hospitalizacijo (povprečno 25 ± 20 dni; $p < 0,001$). Skupna bolnišnična umrljivost je znašala 3,3 % in je bila značilno povezana s številom zapletov ($p < 0,001$).

Zaključek: V času pandemije je prišlo do premika v smeri biliarne etiologije ter višjih vrednosti encimov, kar verjetno odraža zakasnel prihod bolnikov. Umrljivost in dolžina hospitalizacije se nista spremenili. Ključni napovedni dejavnik bolnišnične umrljivosti je bilo število zapletov.

INTRODUCTION

Acute pancreatitis (AP) is an acute inflammation of the gland caused by premature activation of pancreatic enzymes and subsequent tissue autolysis. It is one of the most common acute gastroenterological indications for hospitalisation, with an incidence of 15–80 cases per 100,000 population per year in developed countries. The most common etiological factors are gallstones and alcohol-related damage to the gland, followed by rarer causes such as hypertriglyceridemia, medications, ERCP, and idiopathic cases. The clinical course is highly variable—most patients present with a mild form and have a favourable outcome. Still, approximately 20% of patients develop a severe form with necrosis of the gland, infection, systemic inflammatory response, and multiple organ failure. Mortality in these forms still reaches 15–30% despite advances in diagnostics, modern imaging, early therapeutic procedures, treatment in specialised units, and intensive support (1, 2).

The COVID-19 pandemic caused by SARS-CoV-2 has strained healthcare systems globally and affected the availability and timeliness of emergency and non-emergency medical care. Studies have confirmed increased delays in seeking medical help for acute cardiovascular and surgical diseases, contributing to a higher incidence of complications and poorer outcomes (3). In AP, SARS-CoV-2 may also directly affect the pancreas, as ACE2 receptors, which enable viral entry into cells, are expressed by pancreatic acinar and ductal cells. The literature reports cases of pancreatitis in COVID-19 patients without other known etiological factors (4). Nevertheless, data on the impact of the pandemic on the course and outcomes of treatment of patients with AP remain limited and often contradictory. In a study conducted at the tertiary care department, we compared outcomes among patients with AP during and after the COVID-19 pandemic to assess the pandemic's impact on aetiology, complication rates, treatment success, and mortality. Based on the findings, we sought to identify potential organisational improvements for future similar crises.

The purpose of the study was therefore to obtain data on:

- the frequency and aetiology of AP during and after the COVID-19 pandemic;
- the effectiveness of treatment and mortality among patients with AP during and after the pandemic;
- and the frequency of possible complications and the need for additional treatment in patients with AP in the compared periods.

MATERIALS AND METHODS

In a retrospective, cohort, uncontrolled study, we included patients with clinical and laboratory signs based on which the diagnosis of AP was made, and who were treated at the Gastroenterology Department of the Division of Internal Medicine at the University Medical Centre Maribor in the period from January 1, 2020, to December 31, 2024. We confirmed the diagnosis and aetiology using anamnesis, characteristic clinical presentation, elevated (>3-fold) laboratory markers of pancreatic inflammation (amylase/lipase), and imaging findings. To clarify the aetiology and assess potential complications, we performed chest X-rays to exclude pleural effusion and abdominal ultrasound (US) to evaluate abdominal organs in patients already at the emergency department. When the US was unclear because of intestinal gas or other factors, we performed a contrast-enhanced computed tomography (CT) scan on admission or, as a rule, 2–5 days later, and, in more severe cases, a follow-up contrast-enhanced CT scan during hospitalisation. Abdominal radiologists assessed the degree of morphological change in the gland using a modified Balthazar scale, which evaluates changes according to the following criteria: CT index 0–3 points: mild AP, 4–6 points: moderately severe AP, 7–10 points: severe AP. In cases of suspected choledocholithiasis, we also performed endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP). Endoscopic retrograde cholangiopancreatography (ERCP) with papillotomy was performed no later than 72 hours after confirmation of chole-

docholithiasis, usually within the first 48 hours (5). We obtained all data necessary for analysis from the UKC Maribor medical database.

We collected the data in an Excel spreadsheet, and entered demographic data, habits, number of comorbidities, laboratory test results, number of complications, length of hospitalisation, mortality, and COVID-19 period. The Ethics Committee of the University Medical Centre Maribor approved the study (Decision No. UKC-MB-KME67/24).

We used JASP (version 0.95.4) on a personal computer running Windows 11 for statistical data processing. We presented nominal variables as numbers and frequencies (%) and numerical variables as mean values and standard deviations.

For numerical variables, we first calculated descriptive statistics and checked distribution normality using the Shapiro-Wilk test. Because most numerical variables were not normally distributed, we used non-parametric statistical methods in subsequent analyses.

To analyse the relationship between two nominal variables, we used the chi-square test after first verifying that the conditions for its use were met (i.e., $\geq 80\%$ of cells with an expected frequency ≥ 5). We analysed the relationship between two numerical variables using Spearman's rank correlation test. For numerical-nominal relationships, we used the Mann-Whitney U test or the Kruskal-Wallis test, depending on the number of groups.

We analysed the relationships between nominal and ordinal variables using cross-tabulation tables and reported the results as p-values. We set the significance level at $p < 0.05$. We used logistic regression analysis to assess the impact of selected factors on hospital mortality. We included the effects of the period, comorbidities, and complications on in-hospital mortality. To improve comparability of extreme values, we presented odds ratios (ORs) in a Forest plot on a logarithmic scale with 95% confidence intervals (CIs). The line at $\log(\text{OR}) = 0$ corresponds to $\text{OR} = 1$ and indicates no effect.

RESULTS

During this period, the GI department treated 418 patients with acute pancreatitis. Of these, 223 (53.3%) were diagnosed outside of the COVID-19 period, while 195 (46.7%) were diagnosed inside the COVID-19 period. Outside COVID-19, patients had an average age of 61 years ($SD \pm 16$ years), ranging from 21 to 95 years. During COVID-19, the average age was 61 ($SD \pm 16$), ranging from 21 to 99 years. During the entire observation period, there were 250 men (59.8%) and 168 women (40.2%). Outside of the COVID period, the sex ratio was 142 men (63.7%) to 81 women (36.3%). During the COVID-19 period, the ratio was 108 men (55.4%) to 87 women (44.6%) (Figure 1).

During the COVID-19 pandemic, the average length of hospitalisation was 11.5 days ($SD = 12$), compared with 12 days outside the pandemic. We used Spearman's rank correlation test and found a weak positive association ($\rho = 0.120$; $p = 0.014$) between patients' ages at diagnosis and hospitalisation duration. The COVID-19 period did not significantly affect hospitalisation time ($p = 0.212$) or age at diagnosis ($p = 0.823$).

From the top three most common causes for acute pancreatitis at diagnosis, the most common, per ICD-10 classification based on data from the entire

research period, were gallstones. This aetiology affected 160 patients (38.3%). Idiopathic acute pancreatitis accounted for the second-highest percentage, affecting 119 patients (28.5%), whereas other types of acute pancreatitis ranked third, affecting 75 patients (17.9%). Outside the COVID-19 period, the most common aetiology was undefined acute pancreatitis in 77 patients (34.5%), followed by acute biliary pancreatitis in 71 cases (31.8%) and other types of acute pancreatitis in 40 cases (17.9%).

During the COVID-19 period, acute biliary pancreatitis was the most common aetiology in 89 cases (45.6%), followed by unspecified acute pancreatitis in 42 cases (21.5%) and other acute pancreatitis subtypes in 35 cases (17.9%). We analysed the association between disease aetiology and the COVID-19 period using the chi-square test of independence. We found a statistically significant association ($\chi^2 = 12.53$; $p = 0.028$). The effect size was weak (Cramér's $V = 0.173$). Of all the risk factors included, alcohol consumption was the most common among patients throughout the observation period, occurring in 73 patients (17.5%), closely followed by smoking in 69 patients (16.5%). Drug use was almost absent, occurring in 3 patients (0.7%) (Figure 2).

The study aimed to investigate comorbidity in patients with acute pancreatitis. We classified patients into three categories by number of comorbidities: class I (0 comorbidities), class II (1–3 comorbidities), and class III (> 3 comorbidities). Outside the COVID-19 period, 39 patients (17.5%) fell into the I class, 145 patients (65%) into II class and 39 (17.5%) into III class. During the COVID-19 outbreak, 24 patients (12.3%) classified into I class, 138 patients (70.8%) were classified into II class and 33 patients (16.9%) into III class. The association between the number of comorbidities and the period was not statistically significant ($p = 0.304$), with a very weak correlation (Cramer's $V = 0.075$). (Figure 3).

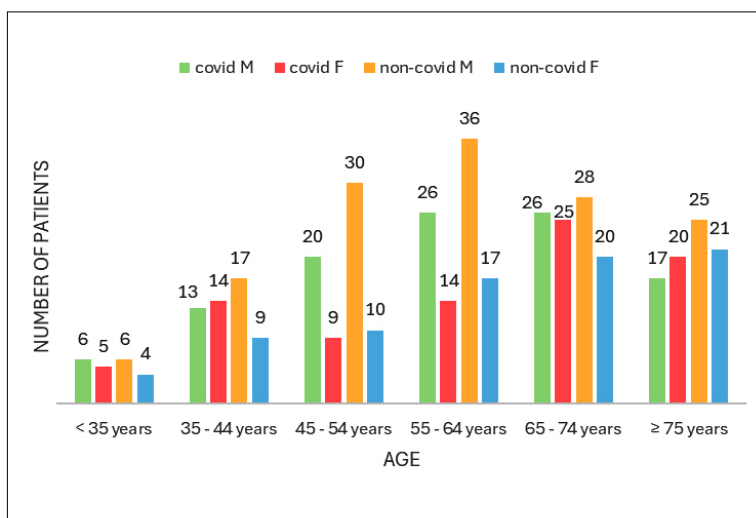


Figure 1: Demographic characteristics of patients with AP, by gender and age distribution.

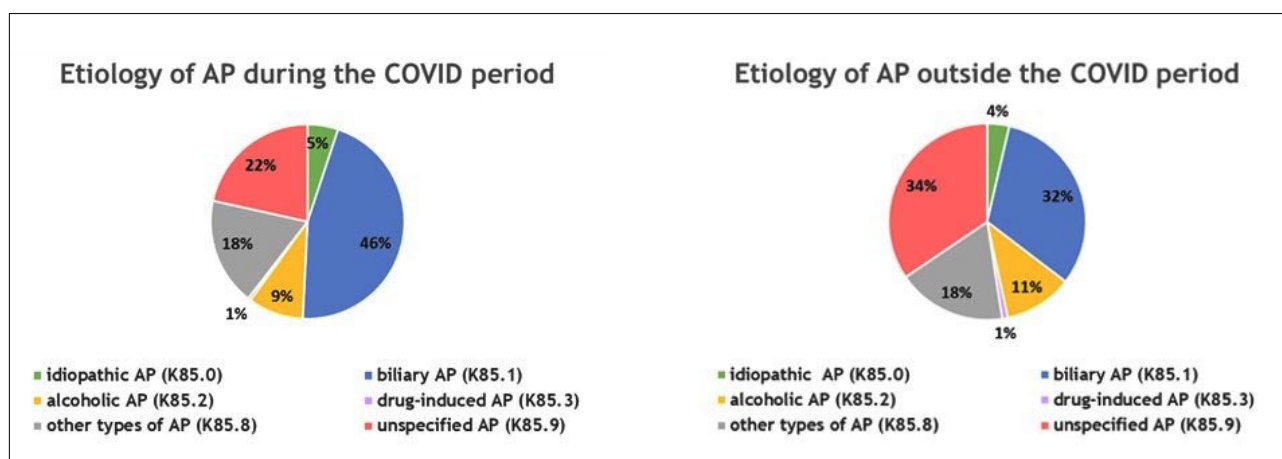


Figure 2: Comparison of the aetiology of AP during and after the COVID-19 pandemic.

Similarly, we monitored complication incidence and classified patients into three categories. Class I (0 complications), class II (1–3 complications), and class III (> 3 complications). Outside the COVID-19 period, 108 patients (48.4%) classified into I class, 85 patients (38.1%) were classified into II class, and 30 patients (13.5%) into III class. During the COVID-19 period, 111 patients (57%) classified into I class, 66 patients (33.8%) into II class, and 18 patients (9.2%) into III class. Among all patients, 27 developed walled-off necrosis (WON), representing 6.46% of the cohort. These patients had a statistically significantly longer average length of hospitalisation ($p < 0.001$). The length of hospitalisation was more than twice as long, with a mean of 25 days ($SD \pm 20$ days). Of the 27 patients who developed WON, 4 (14.8%) were COVID-19 positive. The distribution of complications did not differ significantly

between the two periods ($p = 0.168$), with a very weak association (Cramer's $V = 0.092$). (Figure 4).

For laboratory tests, we closely monitored CRP, calcium, and lipase levels. The CRP level peaked on the third day after diagnosis, with a mean of 172.8 mg/L ($SD \pm 121.1$ mg/L). The two periods did not differ significantly. The Mann-Whitney U test revealed no statistically significant difference between the two periods ($p = 0.077$). Lipase levels differed significantly between periods, with higher values more indicative of acute pancreatitis: the average outside the COVID-19 period was 151.3 μ kat/L ($SD \pm 236.7$ μ kat/L), whereas during the COVID-19 period the average was 227.1 μ kat/L ($SD \pm 281.9$ μ kat/L). The Mann-Whitney U test showed a statistically significant association between period and change in lipase ($p < 0.001$).

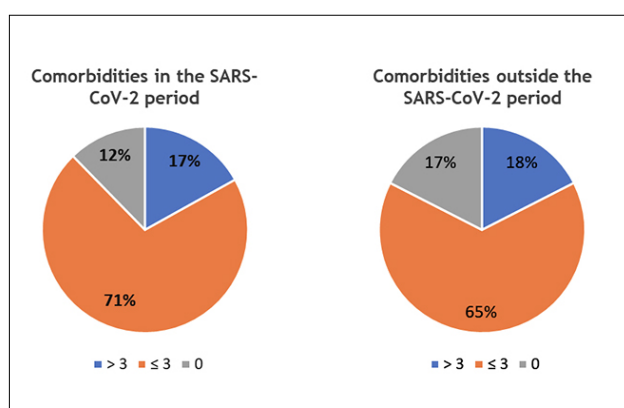


Figure 3: Comparison of comorbidities associated with AP during and after the COVID-19.

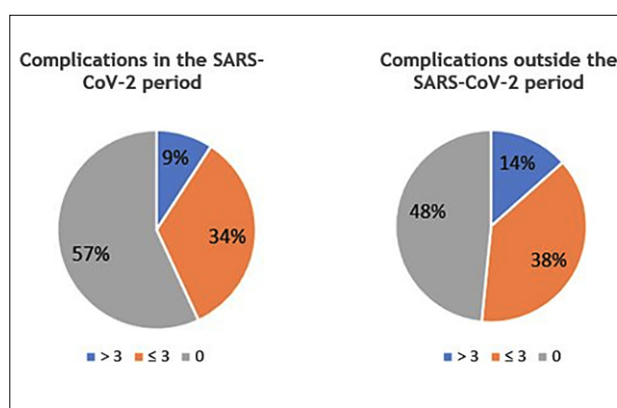


Figure 4: Comparison of complications of AP during and after the COVID-19 pandemic.

As a result of the disease, 14 patients (3.3%) died in hospital, 8 patients (4.1%) during the COVID-19 period, and 6 patients (2.7%) outside the COVID-19 period. Using the chi-square test, we found that hospital mortality was not significantly associated with the COVID-19 period ($\chi^2 = 0.641$, $p = 0.423$), with a very weak association (Cramer's $V = 0.039$). Similarly, there was no statistically significant association between the number of comorbidities and the period ($\chi^2 = 3.718$, $p = 0.156$), with a very weak association (Cramer's $V = 0.094$). However, the number of complications was significantly associated with hospital mortality ($\chi^2 = 24.56$, $p < 0.001$), with a weak correlation (Cramer's $V = 0.242$). We then used a logistic regression to determine the effects of the period, comorbidities, and complications on in-hospital mortality. Logistic regression showed that only complications statistically significantly affected in-hospital mortality ($p < 0.001$; Nagelkerke $R^2 = 0.218$). Patients with 1-3 complications were 9.2 times more likely to die than those without complications ($p = 0.041$), while patients with multiple complications were more than 40 times more likely to die ($p < 0.001$). Forest plot shows OR values on a logarithmic scale with 95% confidence intervals (CI) for better comparability of extreme values.

The line at $\log(OR) = 0$ corresponds to $OR = 1$, indicating no effect (Figure 5).

DISCUSSION

Acute pancreatitis is a serious medical condition that can cause both local and systemic complications and, in the event of complications, is associated with a high mortality rate. The incidence varies by geographic region, often reflecting differences in lifestyle, dietary habits, and specific triggers.

In our study, the epidemiological profile was consistent with the existing literature, with a predominance of males (60%) and a higher incidence in older age groups (> 40 years) (1, 2). The length of hospitalisation did not change significantly between the two periods. The lack of change in hospitalisation length and the statistical insignificance of associations between period and length of hospitalisation, and between age at diagnosis and length of hospitalisation, indicate stable healthcare quality even during the COVID19 pandemic. This contrasts with studies reporting prolonged hospitalisation and limited availability of certain therapeutic procedures due to overcrowding in COVID-19 wards. In our country, the flexibility of healthcare structures and protocols, along with selective patient inclusion, likely played a key role in maintaining quality care even during crises (6, 7).

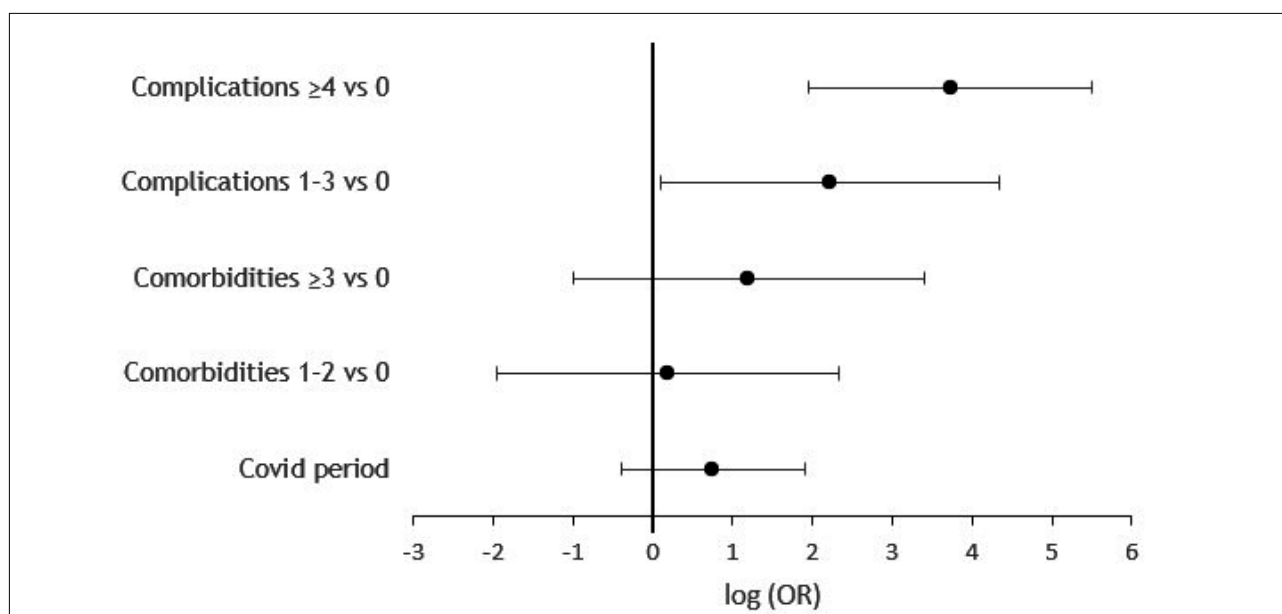


Figure 5: The impact of the specified factors on in-hospital mortality.

According to global literature, the two most important factors for the development of the disease are gallstones and alcohol consumption. Less common causes include metabolic disorders (e.g., elevated blood lipid or calcium levels), parotid gland disorders, viral infections (e.g., Coxsackie, Epstein-Barr, cytomegalovirus, mumps virus), abdominal injuries, and side effects of certain medications. In approximately 10% of patients, the cause cannot be precisely determined; these cases are classified as idiopathic, autoimmune, or hereditary/genetically determined (1, 2, 5, 8, 9, 10).

Determining the aetiology and complications of AP can sometimes be very challenging. In addition to laboratory tests, we use modern imaging modalities such as ultrasound, contrast-enhanced CT, endoscopic ultrasound, and MRCP to clarify the causes, assess the extent of damage to the gland and its immediate surroundings, and evaluate the systemic inflammatory response. In addition to imaging, interleukins and inflammatory markers (IL-6, IL-8, IL-10) provide additional diagnostic support. Both diagnostic procedures are most effective when performed and followed up within 72 hours (5, 10). For detecting choledocholithiasis in AP, abdominal ultrasound has a sensitivity of 50–80% and a specificity of about 90%. The diameter of the common bile duct is an essential additional diagnostic parameter: at a diameter ≤ 3 , the presence of stones is unlikely; at > 4 mm, the possibility increases, and at ≥ 9 mm, choledocholithiasis is very likely (5). EUS is the imaging method best suited to confirm choledocholithiasis with sensitivity and specificity generally exceeding 90% (5). CT plays a central role in cases of suspected necrotising AP. Contrast-enhanced CT (CECT) is essential; however, it often fails to reveal necrotic changes in the early stages. MRCP allows non-invasive imaging of the biliary and pancreatic ducts and is frequently used to exclude choledocholithiasis when cholangitis is absent. Unlike US, which is more sensitive for small stones (< 5 mm), MRCP is non-invasive and less dependent on the examiner's experience.

At present, ERCP is primarily a therapeutic method for diagnosed choledocholithiasis. Current guidelines recommend urgent ERCP in patients with confirmed choledocholithiasis and associated cholangitis, as it enables stone removal from the bile ducts and, if necessary, stent placement. In patients without signs of infection, ERCP is postponed until the inflammation subsides. Early papillotomy, within the first 72 hours of diagnosed choledocholithiasis has been shown to result in a milder course of AP (5).

In Slovenia, emergency ERCP is performed daily, with weekend procedures carried out by interventional endoscopists at the University Department of Gastroenterology at the University Medical Centre Ljubljana. ERCP may also be associated with the development of so-called 'post-ERCP' pancreatitis, which remains the most common complication of the procedure (5, 8, 9, 10, 11, 12, 13).

In our analysis, we observed a significant change in the etiological distribution of AP: biliary pancreatitis predominated during the pandemic, whereas in the post-pandemic period, undefined (idiopathic) pancreatitis was the most common.

In the post-pandemic period, we have observed an increase in reports of AP aetiologies characterised by biliary tract thickening without evident bile obstruction. A possible, and most likely, reason for this is delayed diagnostic evaluation, as the triggering factor in the form of dietary indiscretion, alcohol abuse, or 'memory gaps' in patients may be outdated. Undefined pancreatitis thus encompasses all pancreatitis that cannot be classified with certainty into any of the other etiological groups, even though biliary aetiology may be responsible. This change is relevant and is partly consistent with the findings of Kumar et al. (2021), who also reported a change in the etiological structure due to changes in access to diagnostics and therapy during the pandemic (3). It should be noted that the increase in cases of biliary pancreatitis may also be attributable to delays in elective cholecystectomies and limited access to

primary health care, leading to worsening biliary diseases and a higher incidence of pancreatitis complications (7). We examined how comorbidities affected the course of AP. In both periods, most patients had one to three comorbidities, consistent with our sample's demographic profile, which was predominantly aged over 40 years (1, 2). Statistical analysis showed no statistically significant association between the period and the number of comorbidities. As with complications, according to the MEDIS information system, 95% of patients with AP treated at the University Medical Centre Maribor were managed in the Department of Gastroenterology. In light of this, the sample is representative, and the proportion of patients at risk due to multiple comorbidities and therefore treated in intensive care units is negligible. As with comorbidities, we divided patients with complications into groups; unlike comorbidities, the largest proportion was patients without complications, which is expected, as complications indicate a more severe disease course.

Although we did not find a statistically significant difference in the incidence of complications between the two periods studied, there was a trend toward a slightly lower incidence during the pandemic. This finding needs to be explained in the context of the organisation of treatment, as, as mentioned above, only patients treated in a specialised gastroenterology department were included in our study, where, according to the MEDIS information system, more than 95% of patients with AP are treated at the Division of Internal Medicine at a tertiary institution. Patients with more severe disease who developed complex or life-threatening complications were transferred to internal intensive care or an infectious disease department if they were also COVID-19 positive.

This selection of patients, given that a proportion of patients likely avoided hospitalisation (7), may have contributed to the lower incidence of complications observed in our sample, as patients with more severe disease treated in intensive care units

were excluded from this analysis. This fact is important to consider when interpreting the results, as it may contribute to the apparent lower incidence of complications in the gastroenterology department, whereas more serious complications are recorded elsewhere. Patients with WON complications had a hospitalisation length more than twice as long, at 25 ± 20 days.

A similarly prolonged treatment is also described in the literature: in a retrospective cohort study of patients with large WONs, the authors reported a median hospitalisation duration of 53 days (14). Such discrepancies likely reflect transfers to the intensive care unit, which formally reduced hospitalisation duration because patients were physically present in the intensive care unit, where hospitalisation days are documented separately. For this reason, the actual burden and duration of treatment in patients with WON are likely to be underestimated if only conventional hospital care in the Department of Gastroenterology is considered. In any case, data on patients with WON who require numerous interventional procedures by radiologists and interventional endoscopists, including the insertion of Lumen-Apposing Metal Stents (LAMS) and the removal of necrotic tissue from abdominal cavities, reflect the significant clinical and organisational impact of these complications. The analysis confirms that WON strongly predicts a prolonged, complicated course and more complex treatment. Because of the limited sample size and retrospective design, we cannot reliably assess whether COVID-19 infection directly increases the risk of developing WON. Our analysis and conclusions align with the international literature, which describes cases of pancreatitis with WON complications in COVID-19 primarily as individual cases, without systematic evidence of increased incidence.

CRP values did not differ significantly between the two periods, suggesting that the inflammatory response in AP may not have been directly affected by pandemic conditions but instead reflects individual disease severity (15, 16).

In contrast, average lipase levels during the COVID-19 period were significantly elevated, suggesting more pronounced acute inflammation. A more likely explanation is delayed presentation to healthcare facilities. The literature well documents the link between higher pancreatic enzyme levels and more severe forms of AP (Cho et al., 2023; 16). Our findings align with international literature reporting that the COVID-19 pandemic contributed to delays in seeking medical care, increasing the risk of more serious complications and worsening clinical outcomes (6, 7, 17).

Despite expectations, more advanced logistic regression analysis did not reveal a statistical association between the number of comorbidities and mortality. This result may be because patients with multiple comorbidities and more severe clinical courses are often treated in the intensive care unit or infectious disease department and were therefore not included in our gastroenterology sample. The prevailing view in the literature is that comorbidities contribute to poorer outcomes, particularly with concomitant SARS-CoV-2 infection (18, 19, 20). However, we found that the number of complications was the leading predictor of in-hospital mortality, consistent with prior studies (21, 22).

References

1. Wang CF, Tariq A, Chandra S. Acute Pancreatitis. StatPearls [Internet]. 2025. [cited 2026 Feb 23]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482468/>
2. Skok P, Čeranić D, Krajnc Genslitskaya E. Acute pancreatitis - results of a prospective study. *Zdravniški Vestnik*. 2008; 77(9):573-578.
3. Kumar V, Barkoudah E, Souza DAT, et al. Clinical course and outcome among patients with acute pancreatitis and COVID-19. *European Journal of Gastroenterology & Hepatology*. 2021;33(5):695-700.
4. Liu F, Long X, Zhang B, et al. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. *Clinical Gastroenterology and Hepatology*. 2020;18(9):2128-2130.e2.
5. Čeranić D, Skok P, Zorman M. The role of endoscopic ultrasound and anti-inflammatory cytokines in explaining the aetiology and course of acute pancreatitis. Doctoral dissertation. Faculty of Medicine, University of Ljubljana, 2019.
6. Ramsey ML, Patel A, Sobotka LA, et al. Hospital Trends of Acute Pancreatitis During the Coronavirus Disease 2019 Pandemic. *Pancreas*. 2022;51(5):422-426.
7. Türkylmaz Z, Demirel T, Çakcak İE, et al. What has changed? The impact of the COVID-19 pandemic on the management of acute biliary pancreatitis. *Ulusal Travma ve Acil Cerrahi Dergisi*. 2023;29(10):1167-1174.
8. Thiruvengadam M, Gajendran M, Thiruvengadam S, et al. Acute Pancreatitis. *Disease-a Month*. 2012;58:98-144.
9. Trikudanathan G, Yazici C, Phillips AE, et al. Diagnosis and Management of Acute Pancreatitis. *Gastroenterology*. 2024;167(4):673-688.
10. Tenner S, Vege SS, Sheth S, et al. American College of Gastroenterology guidelines: Management of Acute Pancreatitis. *American Journal of Gastroenterology*. 2024;119:419-437.
11. Clancy TE, Benoit EP, Ashley SW. Current Management of Acute Pancreatitis. *Journal of Gastrointestinal Surgery*. 2005;9(3):440-452.
12. Strang D, Law RJ, Yang D, et al. AGA Clinical Practice Update on the Endoscopic Approach to Recurrent Acute and Chronic Pancreatitis: Expert Review. *Gastroenterology*. 2022;163(4):1107-1114.
13. Dajčman D, Skalicky M, Tošovič Z. Comparison of modern diagnostic methods for gallstones in the common bile duct and guidelines for their stepwise use. *Zdravniški Vestnik*. 2004;73(4):191-5.
14. Ebrahim M, Werge MP, Hadi A, et al. Clinical outcomes following endoscopic or video- assisted retroperitoneal management of acute pancreatitis with large (>15 cm) walled-off pancreatic necrosis: retrospective, single tertiary centre cohort study. *Digestive Endoscopy*. 2022;34(6):1245-1252.
15. Stirling AD, Moran NR, Kelly ME, et al. The predictive value of C-reactive protein (CRP) in acute pancreatitis - is interval change in CRP an additional indicator of severity? *HPB (Oxford)*. 2017;19(10):874-880.
16. Cho IR, Do MY, Han SY, et al. Comparison of Interleukin-6, C-Reactive Protein, Procalcitonin, and the Computed Tomography Severity Index for Early Prediction of Severity of Acute Pancreatitis. *Gut and Liver*. 2022;17(4):629-637.
17. Rădulescu PM, Căluianu EI, Trașcă ET, et al. The Impact of the COVID-19 Pandemic on Outcomes in Acute Pancreatitis: A Propensity Score Matched Study Comparing before and during the Pandemic. *Diagnostics (Basel)*. 2023;13(14):2446.
18. Singh AK, Gillies CL, Singh R, et al. Prevalence of comorbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis. *Diabetes, Obesity Metabolism*. 2020;22(10):1915-1924.
19. Hua S, Yang Y, Zou D, et al. COVID-19 and metabolic comorbidities: An update on emerging evidence for optimal therapies. *Biomedicine & Pharmacotherapy*. 2021;140:111685.
20. Hidalgo NJ, Pando E, Mata R, et al. Impact of comorbidities on hospital mortality in patients with acute pancreatitis: a population-based study of 110,021 patients. *BMC Gastroenterology*. 2023;23(1):81.
21. Selin D, Maret-Ouda J, Oskarsson V, et al. Long-Term Mortality in Acute Pancreatitis-A Population-Based Cohort Study. *United European Gastroenterology Journal*. 2025;13(4):640-649.
22. Yu L, Xie F, Luo L, et al. Clinical characteristics and risk factors of organ failure and death in necrotising pancreatitis. *BMC Gastroenterology*. 2023.



Dejavniki sistemske in črevesne mikrobiote, ki so povezani z nastankom in rezultati zdravljenja raka debelega črevesa in danke

Factors of systemic and intestinal microbiota associated with the development and outcomes of colorectal cancer treatment

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IZVLEČEK

Rak debelega črevesa in danke je ena najpogostejših oblik raka. Poleg genetskih, epigenetskih in dejavnikov življenjskega sloga ima pomembno vlogo pri nastanku in progresu tumorjev debelega črevesa in danke črevesna mikrobiota. S kirurško odstranitvijo tumorja (resekcijo) in drugimi oblikami multimodalnega zdravljenja, vplivamo na spremembo sistemske in črevesne mikrobiote. Identifikacija dejavnikov, s katerimi posegamo v spremembo sistemske in črevesne mikrobiote, lahko pomembno vpliva na rezultate zdravljenja, lokalne in sistemske zaplete povezane z zdravljenjem bolezni, ponovitev bolezni in dolgoročne rezultate zdravljenja. Ko smo pregledali dosegljivo literaturo, ki obravnava dejavnike

ABSTRACT

Colorectal cancer is one of the most common types of cancer worldwide. Beyond genetic, epigenetic, and lifestyle-related factors, the intestinal microbiota plays a significant role in the initiation and progression of colorectal tumours. Surgical tumour removal (resection), along with other multimodal treatments, can substantially alter both the systemic and gut microbiota. Identifying factors that influence these microbiota changes, and understanding alterations in microbial composition, may significantly affect treatment outcomes, local and systemic treatment-related complications, disease recurrence, and long-term prognosis. A review of the available literature on the influence of systemic and gut microbiota on

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vpliva sistemske in črevesne mikrobiote na pojavnost in rezultate zdravljenja raka debelega črevesa in danke, smo ugotovili, da je ta vpliv pomemben za njegov razvoj.

Na pojav bolezni se vpleta preko sistemskega vnetnega odziva, presnovnih dejavnikov, spremembe imunskega odziva, tvorbe karcinogenih dejavnikov ter genskih in epigenetskih sprememb v celicah črevesne sluznice, ki so povezane s proženjem malignih sprememb. Razumevanje pomena imunskih in mikrobiotskih sprememb pri nastanku raka debelega črevesa in danke je pomembno tako za preprečevanje bolezni, kot tudi za razvoj novih strategij zdravljenja. Obetajo se novejši, bolj celostni, individualizirani in posledično uspešnejši pristopi k obravnavi te bolezni.

UVOD

Rak debelega črevesa in danke (RDČD) je ena izmed najpogostejših oblik raka, z zahodnim načinom življenja in prehranjevanja je po incidenci na tretjem mestu, po umrljivosti pa na drugem (1). Na razvoj in napredovanje raka vplivajo številni dejavniki, kot so genetski, presnovni, okolijski ter imunski (2). Pri 80 odstotkih bolnikov z rakom je tekom zdravljenja indicirana operativna odstranitev tumorja. In čeprav to predstavlja na eni strani možnost ozdravitve, pa je čas med operacijo in po njej hkrati čas povečanega tveganja za razvoj rakave bolezni (3), prav metastatska bolezen pa je tista, ki je za večino bolnikov z rakom na koncu usodna. Kirurška manipulacija s tumorskimi celicami infiltriranega tkiva na eni strani (4) ter stresni odgovor telesa na operacijo z vnetjem na drugi strani (5, 6) tumorskim celicam olajšajo prehod skozi tkivne bariere. To jim omogoči pobeg imunskemu sistemu v limfo in kri ter metastaziranje v bezgavke in oddaljena tkiva. Poleg tega odstranitev dela črevesa vpliva na čas prehoda črevesne vsebine, na absorpcijo hranil ter spremeni sestavo črevesne mikrobiote. Raziskave kažejo, da porušena zastopanost črevesnih bakterij, gliv, virusov in

the incidence and treatment outcomes of colorectal cancer indicates that microbiota is an important factor in colorectal carcinogenesis. It contributes to disease development through several mechanisms, including inducing systemic inflammatory responses, altering metabolism, modulating immune function, producing carcinogenic compounds, and promoting genetic and epigenetic changes in the intestinal mucosa associated with malignant transformation. A comprehensive understanding of the immunological and microbiota-related changes involved in colorectal cancer development is essential not only for disease prevention but also for developing novel therapeutic strategies. Emerging approaches are expected to provide more holistic, personalised, and ultimately more effective methods for managing and treating this disease.

arhej (tako imenovana disbioza) sodeluje pri nastanku RDČD. Hkrati je vedno več dokazov, da lahko črevesni mikroorganizmi modificirajo odgovor na zdravljenje kot je kemoterapija in inhibitorji kontrolnih točk (7).

IMUNOST IN RAK DEBELEGA ČREVESEA IN DANKE

Raziskave v zadnjih dveh desetletjih kažejo, da ima imunski sistem tako zaviralni kot spodbujajoči vpliv na razvoj raka, kar imenujemo imunska urejanje raka (angl. immunoediting) (8).

Mehanizmi, ki povzročajo zavoro imunskega odziva pri bolnikih z rakom debelega črevesa in danke

Vpliv tumorja na imunost.

Tumor na različne načine zavira imunski odziv telesa, ki skuša uničiti rakave celice.

Načini, s katerimi to doseže so:

- zavora imunskega odziva, posredovana z imunskimi celicami. Tumorske celice lahko uidejo nadzoru imunskega sistema, s tem da spreminjajo izločanje citokinov in z reprogramiranjem imun-

skih celic, kar deluje zaviralno na imunski sistem in stimulatивно na razvoj raka.

- zavora imunskega odziva, posredovana s celičnimi površinskimi beljakovinami. Primer receptorja oz. površinskega encima na T celicah, dendritičnih celicah in naravnih celicah ubijalkah, ki so pomembni pri raku debelega črevesa in danke je npr. PD-1 (programmed cell death- 1), ki je v kombinaciji PD-L1, katerega izločajo tumorske celice in tumorska stroma, ključni zaviralec citotoksičnega imunskega odziva. Okvara delovanja takih receptorjev omogoča tumorskim celicam, da uidejo imunskemu nadzoru.
- zavora imunskega odziva, posredovana s citokini. Nekateri citokini imunost spodbujajo, drugi pa jo zavirajo. Tumorske celice reprogramirajo status citokinov v prid imunosupresivnih, kar tumorskim celicam omogoča, da se izognejo nadzoru imunskega sistema.
- zavora imunskega odziva, posredovana z motenim delovanjem protitumorskih citokinov. Delovanje citokinov, ki so pomembni za imunost proti rakavim celicam (IL-12, IL-15, IL-24, CXCL9, CXCL10, CXCL11 itd.) je lahko moteno, kar spodbudi nastanek in napredovanje raka.
- obstajajo še nekatere druge oblike zavore imunskega odziva, kot so npr. zavora imunskega odziva posredovana s fosfatazo (zavira aktivacijo T celic), s transkripcijskimi faktorji, presnovnimi spremembami in zavora imunskega odziva, povzročena s tkivno hipoksijo (9).

Sistemska vnetje.

Pri RDČD je sistemska vnetje, za katerega so značilni povišani provnetni citokini in beljakovine akutne faze, pokazatelj slabe prognoze. Mnogi neprijetni simptomi rakave bolezni, kot je povišana telesna temperatura, anemija, utrujenost, izguba apetita in kaheksija so vsaj delno posledica sistemske vnetne reakcije (10). Faktorji, ki sprožijo sistemska vnetje, so posledica interakcij med rakavimi celicami in okolnim tumorskim mikrookoljem, ki vsebuje vnetne celice, fibroblaste, zunajcelični matriks in žile (11). Sistemska vnetje ima številne vplive na progres RDČD, med drugim podpira primarno tumorsko

invazijo, proliferacijo, angiogenezo in metastaziranje ter zavira protitumorsko imunost (10).

Imunosenescenca.

Spremembe v delovanju imunskega sistema, ki nastanejo s staranjem in ki prizadenejo tako prirojen kot pridobljen imunski sistem, pomenijo zmanjševanje sposobnosti imunskega sistema za odziv na patogene dejavnike in zmanjšan nadzor nad rakavimi celicami (12). Kot posledica so starejši ljudje bolj podvrženi razvoju rakavih obolenj, tudi RDČD.

Prehranska podhranjenost.

Bolniki z RDČD imajo zaradi različnih razlogov pogosto zmanjšan vnos hranil. Za dobro delovanje imunskega sistema so potrebna ustrezna mikrohranila, kot so minerali in vitamini ter makrohranila kot so aminokisline, holesterol in maščobne kisline. Posledično njihovo pomanjkanje vodi v oslabil imunski sistem (13). Poleg tega se pri bolnikih z rakom pogosto razvije kaheksija, ki je multifaktorialni katabolni sindrom, za katerega sta značilna progresivna izguba mase skeletnih mišic (z izgubo maščevja ali brez) in sistemsko vnetje, oboje pa ima pomemben vpliv na bolnikovo prirojeno in pridobljeno imunost. (14).

Vpliv operativnega posega na imunski sistem je dvojni.

Najprej nastopi akutna pooperativna zavora imunskega odziva, kasneje, z odstranitvijo tumorja, pa možnost dolgoročne obnove imunosti.

Akutna zavora imunosti.

Resekcija črevesa zaradi raka, v kombinaciji z anestezijo, analgezijo, transfuzijo in infektivnimi zapleti, vodi v aktivacijo stresnega in vnetnega odziva, kar v končni fazi privede v zavrtje sistemske imunosti (15). Operacija zavira celično imunost (T celice, naravne celice ubijalke); vrh tega zavrtja je 3 dni po posegu in traja lahko tudi nekaj tednov po njem. Vzroki za to so številni, od sproščanja rastnih faktorjev (VEGF, PDGF, TGF- β), faktorjev strjevanja krvi, stresnih hormonov (glukokortikoidov, kateho-

laminov) in citokinov (16). Lokalne in sistemske vnetne spremembe ustvarijo dobre pogoje za nastanek premetastatskih niš in za prebuditev spečih rakavih celic (17, 18). Obstajajo ukrepi, ki zmanjšajo perioperativno vnetje in ki jih je priporočljivo v čim večji meri vključiti v obravnavo bolnikov, operiranih zaradi RDČD:

- ERAS. Kirurgija s pospešenim okrevanjem je oblika perioperativne obravnave bolnika, pri kateri z optimizacijo procesov zdravljenja vplivamo na hitrost bolnikovega okrevanja. Ta pristop zmanjšuje perioperativni stres in posledično pooperativno vnetje in umrljivost.
- Kortikosteroidi. Raziskave kažejo na manjši pooperativni sistemski vnetni odgovor in manj zapletov pri bolnikih, ki so prejeli enkratni odmerek kortikosteroida pred operacijo RDČD (19).
- Nesteroidni antirevmatiki. Zmanjšujejo perioperativno vnetje in nižajo potrebo po opioidih, nekatere raziskave pa postavljajo sum na večjo možnost dehiscence anastomoze (20).
- Imunonutricija. Ta naj bi zmanjševala perioperativno vnetje in ugodno vplivala na izhod bolnikov po operaciji gastrointestinalnih rakov (21, 22).
- Intravenska infuzija lidokaina. Perioperativna infuzija lidokaina naj bi ugodno vplivala na imunski odziv bolnika na operacijo, poleg tega zmanjša porabo opioidov in anestetikov (23, 24).

Obnova imunosti.

Odstranitev tumorja in njegovih negativnih učinkov na imunski sistem vodi v manjšo količino imunosupresivnih citokinov ter ponovno okrepitev protitumorskega imunskega odziva. Za boljšo imunost sta nujna tudi ustrezna prehranska podpora ter ukrepi za zmanjšanje stresa (telesna in psihološka rehabilitacija).

Vpliv dodatnega (adjuvantnega) zdravljenja na imunost.

Citotoksična terapija (kemoterapija in radioterapija)

je pogosta terapevtska možnost pri bolnikih z lokalno razširjeno ali metastatsko obliko RDČD.

Najpogostejši neugoden stranski učinek, ki vodi v zavoro sistemske imunosti, je limfopenija (15). Vendar pa lahko obe obliki citotoksičnega zdravljenja hkrati tudi aktivirata sistemske protirakave imunske odzive, ki pomagajo odstraniti oddaljene tumorske celice (25).

Tarčna terapija

se največkrat uporablja pri bolnikih z metastatsko boleznijo RDČD in ima svoj učinek proti raku na eni strani z neposredno inhibicijo signalnih poti ter na drugi s spodbujanjem protitumorske imunosti (26). Slednja se kaže s povečanjem števila cirkulirajočih dendritičnih celic, naravnih celic ubijalk in T celic ter okrepitvijo njihove citotoksičnosti (27, 28).

MIKROBIOTA IN RAK DEBELEGA ČREVEŠA IN DANKE

Mikrobiotske prilagoditve bolnikov z rakom debelega črevesa in danke

Črevesna mikrobiota je kompleksen ekosistem, katerega sestavljajo bakterije (> 99 %), arheje, virusi, glive in paraziti (29) in ki je najbolj skoncentriran v kolonu, zlasti cekumu. Med mikrobioto in gostiteljem obstaja dinamičen, obojestransko koristen odnos: bakterije omogočajo sproščanje nekaterih hranil, tvorbo vitaminov in na druge načine ohranjajo črevesno in sistemsko zdravje ter vplivajo na gostiteljeve imunske in nevroimunske odzive (30), v zameno pa gostitelj mikroorganizmom zagotavlja stabilno okolje in prehranske substrate. Glede na funkcijo jo lahko razdelimo v tri skupine: probiotiki, nevtralne bakterije in škodljive bakterije (31). Probiotiki so koristne bakterije, ki regulirajo imunski sistem, ohranjajo ravnovesje v črevesni mikrobioti, spodbujajo absorpcijo hranil in podpirajo črevesno zdravje (32). Nevtralne bakterije (ali pogojni patogeni) so v normalnih okoliščinah neškodljive, lahko pa pod določenimi pogoji prispevajo k nastanku bolezni. Škodljive bakterije imajo potencial povzročitve bolezni pri gostitelju (33). V zdravem črevesnem mikrobiomu

probiotiki številčno presegajo škodljive bakterije, če pa se ravnotežje poruši, se razrastejo škodljive bakterije, kar vodi v različna bolezenska stanja.

Na sestavo mikrobiote najbolj vpliva arhitekturna zasnova prebavne cevi, zato si je mikrobiom predstavnikov iste vrste bolj podoben kot med predstavniki različnih vrst (34). Pri ljudeh se že zgodaj v življenju začnejo kazati razlike v sestavi črevesne mikrobiote. Po vaginalnem porodu imajo tako novorojenčki več bakterij matrine vaginalne flore, tisti rojeni s carskim rezom pa njene kožne flore (35). Materino mleko vsebuje določene bakterije ter različne bioaktivne sestavine in hranila, ki jih mlečne formule nimajo; pri dojenih novorojenčkih tako prevladujejo *Bifidobacterium* sp., pri nedojenih pa *Enterobacterium* sp. (36).

Sicer pri ljudeh največje razlike v sestavi mikrobiote nastanejo zaradi razlik v prehrani in v življenjskem slogu. Pri osebah, ki jedo več mesa prevladuje *Bacteroides* sp., pri uživanju pretežno rastlinske hrane pa *Prevotella* sp. (37). Razlike nastajajo tudi glede na spol, starost in indeks telesne mase (ITM), in sicer se z debelostjo raznolikost mikrobiote zmanjšuje (38), s starostjo pa se zmanjšuje količina aktinobakterij ter povečuje količina bakteroidet (39). Zaradi uživanja neakovostne hrane, prenajedanja, gastrointestinalnih bolezni (npr. akutni ali kronični gastroenteritis), okolijskih dejavnikov (potovanje v oddaljene destinacije), zdravil (antibiotiki, hormoni, protitumorska zdravila) in staranja se lahko spremeni sestava ter razvije neravnovesje v črevesi mikrobioti (40, 41).

Disbioza je pomembna v patogenezi številnih bolezni črevesa kot so Crohnova bolezen, ulcerozni kolitis pa tudi izven črevesnih stanj kot so sladkorna bolezen tip 2, astma, debelost, avtizem in revmatoidni artritis (42). Zanj je značilno zmanjšanje števila koristnih in povečanje števila provnetnih in prokancerogenih bakterij. Kot kaže, je pomembna tudi v patogenezi RDČD (43). Pri teh bolnikih je bilo namreč zaznati zmanjšano mikrobiotsko raznolikost, poleg tega pa je bila večja

zastopanost firmikutov in fuzobakterij, medtem ko je bila znatno zmanjšana zastopanost proteobakterij (44). Predklinične raziskave kažejo na zmožnost črevesnih bakterij, da vstopajo v interakcijo z epitelom črevesa ter z imunskimi celicami, in sicer tako, da sproščajo različne metabolite, proteine in druge makromolekule, ki regulirajo nastanek raka. Raziskave tudi kažejo, da črevesna mikrobiota lahko modificira odgovor bolnikov na kemoterapijo in imunoterapijo (7).

Spremembe v črevesni mikrobioti pri bolnikih z RDČD.

Značilno je povečano število ustnih patogenov kot so *Fusobacterium nucleatum*, *Parvimonas micra*, *Peptostreptococcus stomatis* itd., nekaterih specifičnih črevesnih bakterij kot so *Bacteroides fragilis*, *Escherichia coli*, *Streptococcus gallolyticus*, *Morganella morganii* ter zmanjšano število koristnih črevesnih bakterij kot so *Streptococcus thermophilus*, *Streptococcus salivarius*, *Lactobacillus gallinarum*, *Clostridium butyricum* in *Carnobacterium maltaromaticum* (7). Poleg spremenjene bakterijske sestave pa naj bi bil z razvojem RDČD ter preživetjem teh bolnikov povezana tudi sprememba črevesnega viroma (45), spremenjena zastopanost gliv in plesni (46) ter arhej (47).

Kako naj bi mikrobná disbioza prispevala k razvoju RDČD.

Možni mehanizmi so proizvodjanje genotoksinov, kar je značilno za *Escherichia coli* (48) in *Campylobacter jejuni* (49), indukcija okvare deoksiribonukleinske kisline (DNK) z akumulacijo reaktivnih kisikovih spojin kot pri *Bacteroides fragilis* (50) in *Enterococcus faecalis* (51), modulacijo onkogenih signalnih poti, kar je značilno za *Fusobacterium nucleatum* (52, 53) ter spodbujanjem vnetja, kar je glavni mehanizem za spodbujanje razvoja raka črevesa pri *Bacteroides fragilis* (54). Pri uživanju hrane, bogate z živalskimi maščobami, je značilna povečana zastopanost bakterij, ki presnavljajo žveplo (55); z njimi je povezano povečano tveganje za razvoj raka debelega črevesa in danke (56), ker tvorijo vodikov sulfid, ki je genotoksičen (57). Nasled-

nji mehanizem, s katerim hrana, bogata z maščobami, povečuje tveganje za nastanek raka, je preko z mikrobi tvorjenih sekundarnih žolčnih kislin kot je deoksiholna kislina (58). Porušen mikrobiom naj bi deloval tudi imunosupresivno, predvsem zaviralno na citotoksične T celice (59).

Črevesni mikrobi izločajo specifične encime, ki omogočajo fermentacijo hranil v obliko, ki se lahko absorbira, npr. neprebavljive ogljikove hidrate v kratkoverižne maščobne kisline (60); slednje imajo tako protivnetne kot imunomodulatorne učinke (61). Poleg kratkoverižnih maščobnih kislin so še drugi bakterijski metabolični produkti, sestavine samih bakterij (npr. lipopolisaharidi), deli njihovih celičnih kapsul in drugi endotoksini, ki učinkujejo na gostitelja. Vplivajo lahko na ohranjanje epitela, tvorbo vitaminov in interakcije z imunskimi celicami (62). Ena od lastnosti mikrobioma je tudi, da regulira prepustnost črevesja. Nekatere vrste bakterij povečujejo prepustnost črevesa. Posledično metaboliti in deli bakterij lažje zapuščajo črevo in vstopajo v krvni sistem, kot vnetni odziv na to pa se sproščajo citokini (63).

Na sestavo črevesne mikrobiote, poleg že naštetega, vplivajo tudi razlike v gostiteljevem genotipu (64). Organizmi imamo ne samo razlike v dednem zapisu, pač pa tudi zmožnost spreminja njegovega izražanja. Gre za epigenetiko, torej za dedne fenotipske spremembe, ki nastanejo brez sprememb v zaporedju nukleinskih kislin. Glavni epigenetski mehanizmi so metilacija DNK (65), modifikacija histonov in posledično remodeliranje kromatina (66) ter delovanja nekodirajočih ribonukleinskih kislin (RNK) (67). Črevesni mikroorganizmi lahko modulirajo metilacijo gostiteljeve DNK in RNK na različne načine, npr. z zagotavljanjem hranil za tvorbo in metabolizem vitaminov, s sintezo poliaminov (ti so ključni za proliferacijo celic, regulacijo genov, stresni odgovor), s tvorbo kratkoverižnih maščobnih kislin in s sproščanjem ekstracelularnih vezikul, ki so napolnjene z regulatornimi molekulami (68).

Na nastanek in progres raka lahko črevesni mikroorganizmi vplivajo tudi s presnovo različnih rakot-

vornih snovi – karcinogenov (69), in sicer ga na takšen način lahko bodisi spodbujajo ali pa zavirajo (70). Eden od glavnih mehanizmov je z modulacijo aktivnosti encimov, ki sodelujejo pri aktivaciji ali deaktivaciji karcinogenov, s čimer vplivajo na biorazpoložljivost in njihovo toksičnost (71). Z vzdrževanjem zdrave črevesne mikrobiote lahko tako zmanjšamo vpliv karcinogenov in s tem zmanjšamo tveganje za razvoj raka.

Homeostaza energije z absorpcijo, shranjevanjem in porabo energije iz prehranskega vnosa (72) je prav tako pod vplivom črevesne mikrobiote. Uravnava namreč presnovne hormone in dele možganov, ki regulirajo prehranjevalno vedenje (73). Tako imenovana črevesna mikrobiota – možganska os je obojesmerna signalna os, ki regulira telesno težo z uravnavanjem apetita ter porabo in shranjevanjem energije (74). Ob tem je tako za debelost kot podhranjenost značilen isti biološki faktor, to je sprememba v sestavi in raznolikosti črevesne mikrobiote glede na zdrave posameznike (75, 76).

Spremembe v življenjskem slogu in presežek hrane sta pomembna faktorja za porast debelosti. Povečano uživanje hrane z visoko vsebnostjo maščob in sladkorja dokazano spremeni mikrobno ekologijo, za katero je značilna zmanjšana mikrobna raznolikost. Ta sprememba ima za posledico spremembo v sestavi kratkoverižnih maščobnih kislin, v homeostazi energije ter povečanem vnetju (77). Znano je, da je debelost povezana z blagim kroničnim vnetjem in inzulinsko rezistenco (78). Eden od razlogov za to vnetje je med drugim povečana prepustnost črevesa in posledična translokacije po Gramu negativnih bakterij in njenih sestavnih delov v kri.

Študije črevesne mikrobiote pri podhranjenih so bile v veliki večini primerov narejene bodisi pri podhranjenih otrocih ali bolnikih z anoreksijo nervozo. Za oboje so značilne spremembe v sestavi črevesne mikrobiote, in sicer zmanjšanje celokupne količine bakterij in zmanjšana njihova raznolikost (79). Po pridobitvi na teži je mikrobna

raznolikost porasla, vendar pa so se ohranile določene motnje v njeni sestavi in spremenjen profil kratkoverižnih maščobnih kislin v blatu.

Še bolj kompleksne mehanizme in vplive črevesne mikrobiote na gostiteljevo zdravje lahko opazujemo pri bolnikih s kaheksijo. Kaheksija je uničujoč proces, ki pogosto prizadene tudi bolnike z RDČD. Gre za presnovni sindrom, za katerega je značilna ne le izguba telesne teže pač pa tudi pospešena razgradnja maščobnega tkiva in izguba skeletnih mišic. Domnevni patofiziološki mehanizmi pri njenem nastanku so sistemski vnetni odgovor, spremenjen energijski metabolizem, malabsorpcija, anoreksija in nevroendokrine spremembe (80). Za razliko od običajnega hujšanja, pri katerem telo skuša varčevati z energijo, pri kaheksiji telo energijo porablja hitreje kot običajno. Verjetno je najpomembnejši dejavnik pri nastanku kaheksije sistemsko vnetje. Rakave celice in bolnikov imunski sistem sproščajo citokine (npr. $\text{TNF-}\alpha$, IL-6, IL-1, $\text{INF-}\gamma$), ki telesu naročajo razgradnjo mišic in lipolizo (81). S tem pride do uničevanja skeletnih mišic z namenom sproščanja aminokislin ter do črpanja maščobnih zalog, ki jih telo ne more učinkovito obnavljati. Poleg tega jetra pod vplivom vnetja proizvajajo namesto koristnih beljakovin, kot je albumin, beljakovine akutne faze, kar je energijsko potratno. Vnetni citokini potujejo preko krvno-možganske pregrade in izklopijo center za lakoto ter vklopijo center za sitost, zaradi česar bolniki nimajo apetita. Anoreksija poslabša negativno energijsko ravnovesje in dodatno prispeva k propadanju tkiv (82).

Nastale spremembe pri kaheksiji rakavih bolnikov imajo za bolnika številne posledice, ki vključujejo zmanjšano kakovost življenja (utrujenost, šibkost), slabšo toleranco za zdravljenje in zmanjšano preživetje (83). Kaheksija otežuje zdravljenje s kemoterapijo, saj pogosto zahteva prilagajanje shem in znižanje odmerkov zdravil, kar na koncu vpliva na izide zdravljenja (84). Raziskave kažejo, da pride pri kaheksiji do pomembnih sprememb tudi v črevesni mikrobioti. Znano je, da igra črevesna mikro-

biota pomembno vlogo pri modulaciji imunskega sistema, absorpciji hranil, ohranjanju integritete črevesa in uravnavanju različnih fizioloških procesov, kot so prebava, metabolizem in zaščita pred patogeni. Disbioza lahko moti presovno homeostazo gostitelja, kar vodi do spremenjenega energijskega ravnovesja, motene absorpcije hranil in vnetja, kar prispeva k napredovanju kaheksije (85).

Predklinične in klinične študije kažejo, da imajo kahektični bolniki spremembe v raznolikosti (ta je zmanjšana), sestavi in delovanju črevesnega mikrobioma (86), moteno pa je tudi delovanje črevesne pregrade (87). Pri kaheksiji zaradi raka je izguba mišične mase tesno povezana tudi z disbiozo črevesne mikrobiote. Spremembe imajo za posledico značilno zmanjšano proizvodnjo kratkoverižnih maščobnih kislin; zlasti so za ohranjanje celovitosti črevesne pregrade, uravnavanje vnetja ter modulacijo mišične presnove ključne butirat, acetat in propionat (88, 89). Glede na pomembno vlogo kratkoverižnih maščobnih kislin predstavlja obnova ravnovesja črevesne mikrobiote in proizvodnje kratkoverižnih maščobnih kislin obetavno terapevtsko pot za preprečevanje kaheksije (85, 89). Študije, ki trenutno potekajo, proučujejo učinkovitost probiotikov, prebiotikov in presaditve fekalne mikrobiote na izboljšanje stanja bolnikov, ki ob rakavi bolezni trpijo zaradi kaheksije.

Vpliv operativnega posega na črevesno mikrobioto

Operacija debelega črevesa in danke lahko bistveno spremeni sestavo črevesne mikrobiote. Razlogov za to je več, med drugim so to mehansko čiščenje črevesa, perioperativna uporaba antibiotikov, spremenjena anatomija črevesa, pooperativna prehrana in stres. Raziskave so po operacijah RDČD pokazale zmanjšano število bakteroidet in firmikutov ter povečanje števila proteobakterij (90), celokupno zmanjšanje števila bakterij in najpogostejših obligatornih anaerobov ter povečano zastopanost enterobakterij, stafilokokov, *Pseudomonas* sp. in *Clostridium difficile* (91).

Odstranitev dela črevesa spremeni lokalne pogoje kot so pH, peristaltika in dostop do hranil. Uporaba antibiotikov zmanjša raznolikost črevesne mikrobiote in omogoči razrast patogenih bakterij kot je *Clostridium difficile*. Čas antimikrobne profilakse naj bo zato čim krajši, poleg tega je vprašljiva dolgoročna dobrobit predoperativne oralne antibiotične priprave črevesa na operacijo RDČD.

Uporaba opioidov negativno vpliva na črevesni mikrobiom z zmanjšanjem raznolikosti ter števila koristnih mikroorganizmov, kot so laktobacili in bifidobakterije (92). To je, poleg že znanih negativnih vplivov opioidov na povrnitev peristaltike, povzročanje slabosti in bruhanja, zakasnjene rehabilitacije in drugih, še dodaten razlog za čim manjšo uporabo opioidov pri operacijah RDČD.

Parenteralna hrana spreminja črevesno mikrobioto, in sicer spodbuja razrast bakterij, ki lažje prenašajo stanje brez hranil, kot so proteobakterije in zavira razrast firmikutov, ki dominirajo v okolju bogatem s hranili (93). Enteralna prehrana podpira obnovo črevesne mikrobiote in je zato pomembno z njo prenehati čim kasneje pred ter z njo nadaljevati čim prej po operaciji.

Nekateri dokazi nakazujejo, da celo anestezija (94) in hipotermija (95) med posegom neželeno spreminjata sestavo in raznolikost črevesne mikrobiote. To poudarja potrebo po manj invazivnih kirurških tehnikah, s krajšim časom, ki je potreben za anestezijo bolnika ter medoperativni ukrepi za zmanjšanje tveganja za podhladitev bolnika.

ZAKLJUČEK

RDČD predstavlja eno najpogostejših oblik rakave bolezni v zahodnem svetu, njena pojavnost pa je zaradi načina življenja in prehranjevanja v porastu. Imunski odziv in črevesne mikrobiotske prilagoditve se vedno bolj kažejo kot pomemben dejavnik, tako pri nastanku, kot tudi pri zdravljenju te smrtonosne bolezni. Gre za dinamičen in medsebojno povezan proces, ki se pomembno spremeni

po kirurškem posegu. Imunski sistem ima pomembno vlogo pri zavori nastanka tumorjev. Kadar je njegovo delovanje okrnjeno, kar se zgodi tudi perioperativno, lahko to rakave celice izkoristijo za lastno preživetje. Zaradi interakcij med tumorjem in okolnimi tkivi se izločajo faktorji, ki sprožijo nastanek sistemskega vnetja. Kadar je vnetni odgovor pretiran, pospešuje razvoj raka skozi več dobro znanih mehanizmov. Zato priporočajo uporabo protivnetnih strategij, kot je perioperativna uporaba enkratnega visokega odmerka kortikosteroidov ali medoperativna intravenska infuzija lido-kaina ter obravnava bolnikov v skladu s principi kirurgije s pospešenim okrevanjem (ERAS).

Zadnja leta je vedno bolj jasno, da je za zdravje črevesa zelo pomembna njegova mikrobiota. Tako kot lahko njena disbioza povzroči nastanek različnih obolenj, tudi raka, pa njeno porušeno ravnovesje slabo vpliva tudi na celjenje ran in končni izhod po operaciji. Nezdrava prehrana je le eden od dejavnikov za neustrezno zastopanost bakterij v črevesni mikrobioti, za katero je značilno zmanjšana raznolikost ter povečano število provnetnih in prokancerogenih mikrobov. Čeprav z namenom ozdravitve, lahko operacija, predoperativni ukrepi, antibiotiki in celo anestezija neugodno vplivajo na črevesno mikrobioto, njena spremenjena sestava in perioperativni stres in vnetje pa zaostalim tumorskim celicam lahko olajšajo prehod čez tkivne bariere v kri in limfo.

Raziskovanje in razumevanje pomena imunskih in mikrobiotskih sprememb že ima določen vpliv na razvijanje novih strategij zdravljenja. V prihodnosti bi lahko pomenil nove metode za zgodnejše odkrivanje bolezni ter bolj učinkovito in bolniku prilagojeno onkološko zdravljenje. Nova dognanja na tem področju bodo usmerila na najprimernejšo prehransko predoperativno in pooperativno podporo, medoperativne strategije in ukrepe za podporo imunskemu sistemu in ohranjanju zdrave mikrobiote, kar bi kot sveženj ukrepov lahko imelo ugoden učinek na zdravljenje in preživetje bolnikov z RDČD.

Reference

- Bray F, Laversanne M, Sung H, Ferlay J, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024 May-Jun;74(3):229-263.
- Eng C, Yoshino T, Ruiz-García E, et al. Colorectal cancer. *Lancet*. 2024 Jul 20;404(10449):294-310. 3.
- Demicheli R, Retsky MW, Hrushesky WJ, et al. The effects of surgery on tumor growth: a century of investigations. *Ann Oncol*. 2008 Nov;19(11):1821-8. 4.
- Coffey JC, Wang JH, Smith MJ, et al. Excisional surgery for cancer cure: therapy at a cost. *Lancet Oncol*. 2003 Dec;4(12):760-8.
- Angele MK, Faist E. Clinical review: immunodepression in the surgical patient and increased susceptibility to infection. *Crit Care*. 2002 Aug;6(4):298-305.
- Tang F, Tie Y, Tu C, et al. Surgical trauma-induced immunosuppression in cancer: Recent advances and the potential therapies. *Clin Transl Med*. 2020 Jan;10(1):199-223.
- Wong CC, Yu J. Gut microbiota in colorectal cancer development and therapy. *Nat Rev Clin Oncol*. 2023 Jul;20(7):429-452.
- Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science*. 2011 Mar 25;331(6024):1565-70.
- Zhang Y, Rajput A, Jin N, et al. Mechanisms of Immunosuppression in Colorectal Cancer. *Cancers (Basel)*. 2020 Dec 20;12(12):3850.
- Tuomisto AE, Mäkinen MJ, Väyrynen JP. Systemic inflammation in colorectal cancer: Underlying factors, effects, and prognostic significance. *World J Gastroenterol*. 2019 Aug 21;25(31):4383-4404.
- McAllister SS, Weinberg RA. The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis. *Nat Cell Biol*. 2014 Aug;16(8):717-27.
- Wang Y, Cao X, Yang C, et al. Ferroptosis and immunosenescence in colorectal cancer. *Semin Cancer Biol*. 2024 Nov;106-107:156-165.
- Munteanu C, Schwartz B. The relationship between nutrition and the immune system. *Front Nutr*. 2022 Dec 8;9:1082500.
- Rounis K, Makrakis D, Gioulbasanis I, et al. Cancer Cachexia and Antitumor Immunity: Common Mediators and Potential Targets for New Therapies. *Life (Basel)*. 2022 Jun 12;12(6):880.
- Li C, Li J. Dysregulation of systemic immunity in colorectal cancer and its clinical applications as biomarkers and therapeutics. *Crit Rev Oncol Hematol*. 2024 Dec;204:104543.
- Bakos O, Lawson C, Rouleau S, et al. Combining surgery and immunotherapy: turning an immunosuppressive effect into a therapeutic opportunity. *J Immunother Cancer*. 2018 Sep 3;6(1):86.
- Peinado H, Zhang H, Matei IR, et al. Pre-metastatic niches: organ-specific homes for metastases. *Nat Rev Cancer*. 2017 May;17(5):302-317.
- Alieva M, van Rheeën J, Broekman MLD. Potential impact of invasive surgical procedures on primary tumor growth and metastasis. *Clin Exp Metastasis*. 2018 Apr;35(4):319-331.
- McSorley ST, Roxburgh CSD, Horgan PG, et al. The Impact of Preoperative Dexamethasone on the Magnitude of the Postoperative Systemic Inflammatory Response and Complications Following Surgery for Colorectal Cancer. *Ann Surg Oncol*. 2017 Aug;24(8):2104-2112.
- Hakkarainen TW, Steele SR, Bastaworous A, et al. Nonsteroidal anti-inflammatory drugs and the risk for anastomotic failure: a report from Washington State's Surgical Care and Outcomes Assessment Program (SCOAP). *JAMA Surg*. 2015 Mar 1;150(3):223-8.
- Buzquurz F, Bojesen RD, Grube C, et al. Impact of oral preoperative and perioperative immunonutrition on postoperative infection and mortality in patients undergoing cancer surgery: systematic review and meta-analysis with trial sequential analysis. *BJS Open*. 2020 Oct;4(5):764-775.
- Niu JW, Zhou L, Liu ZZ, et al. A Systematic Review and Meta-Analysis of the Effects of Perioperative Immunonutrition in Gastrointestinal Cancer Patients. *Nutr Cancer*. 2021;73(2):252-261.
- Chamaraux-Tran TN, Piegeler T. The Amide Local Anesthetic Lidocaine in Cancer Surgery-Potential Antimetastatic Effects and Preservation of Immune Cell Function? A Narrative Review. *Front Med (Lausanne)*. 2017 Dec 20;4:235.
- Weibel S, Jokinen J, Pace NL, et al. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. *Br J Anaesth*. 2016 Jun;116(6):770-83.
- Huang KC, Chiang SF, Chang HY, et al. Colorectal cancer-specific IFN β delivery overcomes dysfunctional dsRNA-mediated type I interferon signaling to increase the abscopal effect of radiotherapy. *J Immunother Cancer*. 2024 May 15;12(5):e008515.
- Xie YH, Chen YX, Fang JY. Comprehensive review of targeted therapy for colorectal cancer. *Signal Transduct Target Ther*. 2020 Mar 20;5(1):22.
- Botta C, Bestoso E, Apollinari S, et al. Immune-modulating effects of the newest cetuximab-based chemoimmunotherapy regimen in advanced colorectal cancer patients. *J Immunother*. 2012 Jun;35(5):440-7.
- Chen S, Li X, Chen R, et al. Cetuximab intensifies the ADCC activity of adoptive NK cells in a nude mouse colorectal cancer xenograft model. *Oncol Lett*. 2016 Sep;12(3):1868-1876.
- Perler BK, Friedman ES, Wu GD. The Role of the Gut Microbiota in the Relationship Between Diet and Human Health. *Annu Rev Physiol*. 2023 Feb 10;85:449-468.
- Jandhyala SM, Talukdar R, Subramanyam C, et al. Role of the normal gut microbiota. *World J Gastroenterol*. 2015 Aug 7;21(29):8787-803.
- Szajewska H, Scott KP, de Meij T, et al. Antibiotic-perturbed microbiota and the role of probiotics. *Nat Rev Gastroenterol Hepatol*. 2025 Mar;22(3):155-172.
- Gao T, Wang X, Li Y, et al. The Role of Probiotics in Skin Health and Related Gut-Skin Axis: A Review. *Nutrients*. 2023 Jul 13;15(14):3123.
- Lembke HK, Carlson EE. Activity-based probes in pathogenic bacteria: Investigating drug targets and molecule specificity. *Curr Opin Chem Biol*. 2023 Oct;76:102359.
- Hall AB, Tolonen AC, Xavier RJ. Human genetic variation and the gut microbiome in disease. *Nat Rev Genet*. 2017 Nov;18(11):690-699.
- Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A*. 2010 Jun 29;107(26):11971-5.
- Matamoros S, Gras-Leguen C, Le Vacon F, et al. Development of intestinal microbiota in infants and its impact on health. *Trends Microbiol*. 2013 Apr;21(4):167-73.
- Hartstra AV, Bouter KE, Bäckhed F, et al. Insights into the role of the microbiome in obesity and type 2 diabetes. *Diabetes Care*. 2015 Jan;38(1):159-65.
- Yun Y, Kim HN, Kim SE, et al. Comparative analysis of gut microbiota associated with body mass index in a large Korean cohort. *BMC Microbiol*. 2017 Jul 4;17(1):151.
- Odamaki T, Kato K, Sugahara H, et al. Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. *BMC Microbiol*. 2016 May 25;16:90.
- Dapa T, Xavier KB. Effect of diet on the evolution of gut commensal bacteria. *Gut Microbes*. 2024 Jan-Dec;16(1):2369337.
- Ghosh TS, Shanahan F, O'Toole PW. The gut microbiome as a modulator of healthy ageing. *Nat Rev Gastroenterol Hepatol*. 2022 Sep;19(9):565-584.

- 42.Spor A, Koren O, Ley R. Unravelling the effects of the environment and host genotype on the gut microbiome. *Nat Rev Microbiol.* 2011 Apr;9(4):279-90.
- 43.Singh G, Chaudhry Z, Boyadzhyan A, et al. Dysbiosis and colorectal cancer: conducive factors, biological and molecular role, and therapeutic perspectives. *Explor Target Antitumor Ther.* 2025 Jun 27;6:1002329.
- 44.Gao Z, Guo B, Gao R, et al. Microbiota disbiosis is associated with colorectal cancer. *Front Microbiol.* 2015 Feb 2;6:20.
- 45.Nakatsu G, Zhou H, Wu WKK, et al. Alterations in Enteric Virome Are Associated With Colorectal Cancer and Survival Outcomes. *Gastroenterology.* 2018 Aug;155(2):529-541.e5.
- 46.Coker OO, Nakatsu G, Dai RZ, et al. Enteric fungal microbiota dysbiosis and ecological alterations in colorectal cancer. *Gut.* 2019 Apr;68(4):654-662.
- 47.Coker OO, Wu WKK, Wong SH, et al. Altered Gut Archaea Composition and Interaction With Bacteria Are Associated With Colorectal Cancer. *Gastroenterology.* 2020 Oct;159(4):1459-1470.e5.
- 48.Johnson WM, Lior H. A new heat-labile cytolethal distending toxin (CLDT) produced by *Escherichia coli* isolates from clinical material. *Microb Pathog.* 1988 Feb;4(2):103-13.
- 49.He Z, Gharaibeh RZ, Newsome RC, et al. *Campylobacter jejuni* promotes colorectal tumorigenesis through the action of cytolethal distending toxin. *Gut.* 2019 Feb;68(2):289-300.
- 50.Goodwin AC, Destefano Shields CE, Wu S, et al. Polyamine catabolism contributes to enterotoxigenic *Bacteroides fragilis*-induced colon tumorigenesis. *Proc Natl Acad Sci U S A.* 2011 Sep 13;108(37):15354-9.
- 51.Wang X, Huycke MM. Extracellular superoxide production by *Enterococcus faecalis* promotes chromosomal instability in mammalian cells. *Gastroenterology.* 2007 Feb;132(2):551-61.
- 52.Rubinstein MR, Wang X, Liu W, et al. *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/ β -catenin signaling via its FadA adhesin. *Cell Host Microbe.* 2013 Aug 14;14(2):195-206.
- 53.Rubinstein MR, Baik JE, Lagana SM, et al. *Fusobacterium nucleatum* promotes colorectal cancer by inducing Wnt/ β -catenin modulator Annexin A1. *EMBO Rep.* 2019 Apr;20(4):e47638.
- 54.Chung L, Thiele Orberg E, Geis AL, et al. *Bacteroides fragilis* Toxin Coordinates a Pro-carcinogenic Inflammatory Cascade via Targeting of Colonic Epithelial Cells. *Cell Host Microbe.* 2018 Feb 14;23(2):203-214.e5.
- 55.David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* 2014 Jan 23;505(7484):559-63.
- 56.Nguyen LH, Ma W, Wang DD, et al. Association Between Sulfur-Metabolizing Bacterial Communities in Stool and Risk of Distal Colorectal Cancer in Men. *Gastroenterology.* 2020 Apr;158(5):1313-1325.
- 57.Attene-Ramos MS, Nava GM, Muellner MG, et al. DNA damage and toxicogenomic analyses of hydrogen sulfide in human intestinal epithelial FHs 74 Int cells. *Environ Mol Mutagen.* 2010 May;51(4):304-14.
- 58.Garrett WS. Cancer and the microbiota. *Science.* 2015 Apr 3;348(6230):80-6.
- 59.Peucker K, Strigli A, Tauriello DVF, et al. Microbiota-dependent activation of the myeloid calcineurin-NFAT pathway inhibits B7H3- and B7H4-dependent anti-tumor immunity in colorectal cancer. *Immunity.* 2022 Apr 12;55(4):701-717.e7.
- 60.Flint HJ, Scott KP, Duncan SH, et al. Microbial degradation of complex carbohydrates in the gut. *Gut Microbes.* 2012 Jul-Aug;3(4):289-306.
- 61.Tan J, McKenzie C, Potamitis M, et al. The role of short-chain fatty acids in health and disease. *Adv Immunol.* 2014;121:91-119.
- 62.Gilbert JA, Blaser MJ, Caporaso JG, et al. Current understanding of the human microbiome. *Nat Med.* 2018 Apr 10;24(4):392-400.
- 63.Brandma E, Kloosterhuis NJ, Koster M, et al. A Proinflammatory Gut Microbiota Increases Systemic Inflammation and Accelerates Atherosclerosis. *Circ Res.* 2019 Jan 4;124(1):94-100.
- 64.Goodrich JK, Davenport ER, Clark AG, et al. The Relationship Between the Human Genome and Microbiome Comes into View. *Annu Rev Genet.* 2017 Nov 27;51:413-433.
- 65.Niu Y, Zhao X, Wu YS, et al. N6-methyl-adenosine (m6A) in RNA: an old modification with a novel epigenetic function. *Genomics Proteomics Bioinformatics.* 2013 Feb;11(1):8-17.
- 66.Maunakea AK, Chepelev I, Zhao K. Epigenome mapping in normal and disease States. *Circ Res.* 2010 Aug 6;107(3):327-39.
- 67.Mangiavacchi A, Morelli G, Orlando V. Behind the scenes: How RNA orchestrates the epigenetic regulation of gene expression. *Front Cell Dev Biol.* 2023 Jan 25;11:1123975.
- 68.Rubas NC, Torres A, Maunakea AK. The Gut Microbiome and Epigenomic Reprogramming: Mechanisms, Interactions, and Implications for Human Health and Disease. *Int J Mol Sci.* 2025 Sep 5;26(17):8658.
- 69.Qu R, Zhang Y, Ma Y, et al. Role of the Gut Microbiota and Its Metabolites in Tumorigenesis or Development of Colorectal Cancer. *Adv Sci (Weinh).* 2023 Aug;10(23):e2205563.
- 70.Ludgate ME, Masetti G, Soares P. The relationship between the gut microbiota and thyroid disorders. *Nat Rev Endocrinol.* 2024 Sep;20(9):511-525.
- 71.Greten FR, Arkan MC. Gut microbial carcinogen metabolism: another avenue to cancer. *Signal Transduct Target Ther.* 2024 Oct 28;9(1):297.
- 72.Bakker GJ, Zhao J, Herrema H, et al. Gut Microbiota and Energy Expenditure in Health and Obesity. *J Clin Gastroenterol.* 2015 Nov-Dec;49 Suppl 1:S13-9.
- 73.Kairupan TS, Amitani H, Cheng KC, et al. Role of gastrointestinal hormones in feeding behavior and obesity treatment. *J Gastroenterol.* 2016 Feb;51(2):93-103.
- 74.Bauer PV, Hamr SC, Duca FA. Regulation of energy balance by a gut-brain axis and involvement of the gut microbiota. *Cell Mol Life Sci.* 2016 Feb;73(4):737-55.
- 75.Gordon JI, Dewey KG, Mills DA, et al. The human gut microbiota and undernutrition. *Sci Transl Med.* 2012 Jun 6;4(137):137ps12.
- 76.Ley RE, Turnbaugh PJ, Klein S, et al. Microbial ecology: human gut microbes associated with obesity. *Nature.* 2006 Dec 21;444(7122):1022-3.
- 77.de Clercq NC, Groen AK, Romijn JA, et al. Gut Microbiota in Obesity and Undernutrition. *Adv Nutr.* 2016 Nov 15;7(6):1080-1089.
- 78.Odegaard JI, Chawla A. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. *Science.* 2013 Jan 11;339(6116):172-7.
- 79.Morita C, Tsuji H, Hata T, et al. Gut Dysbiosis in Patients with Anorexia Nervosa. *PLoS One.* 2015 Dec 18;10(12):e0145274.
- 80.Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. *Nat Rev Clin Oncol.* 2013 Feb;10(2):90-9.
- 81.Panebianco C, Villani A, Potenza A, et al. Targeting Gut Microbiota in Cancer Cachexia: Towards New Treatment Options. *Int J Mol Sci.* 2023 Jan 17;24(3):1849.
- 82.Peixoto da Silva S, Santos JMO, Costa E Silva MP, et al. Cancer cachexia and its pathophysiology: links with sarcopenia, anorexia and asthenia. *J Cachexia Sarcopenia Muscle.* 2020 Jun;11(3):619-635.
- 83.Aoyagi T, Terracina KP, Raza A, et al. Cancer cachexia, mechanism and treatment. *World J Gastrointest Oncol.* 2015 Apr 15;7(4):17-29.
- 84.Baracos VE, Martin L, Korc M, et al. Cancer-associated cachexia. *Nat Rev Dis Primers.* 2018 Jan 18;4:17105.

85. Ziemons J, Smidt ML, Damink SO, et al. Gut microbiota and metabolic aspects of cancer cachexia. *Best Pract Res Clin Endocrinol Metab.* 2021 May;35(3):101508.
86. Ni Y, Lohinai Z, Heshiki Y, et al. Distinct composition and metabolic functions of human gut microbiota are associated with cachexia in lung cancer patients. *ISME J.* 2021 Nov;15(11):3207-3220.
87. Malard F, Vekhoff A, Lapusan S, et al. Gut microbiota diversity after autologous fecal microbiota transfer in acute myeloid leukemia patients. *Nat Commun.* 2021 May 25;12(1):3084.
88. Liu H, Cheng Y, Qu Y, et al. Unraveling the gut microbiota and short-chain fatty acids characteristics and associations in a cancer cachexia mouse model. *Microb Pathog.* 2023 Oct;183:106332.
89. Pérez-Reytor D, Puebla C, Karahanian E, et al. Use of Short-Chain Fatty Acids for the Recovery of the Intestinal Epithelial Barrier Affected by Bacterial Toxins. *Front Physiol.* 2021 May 24;12:650313.
90. Deng X, Li Z, Li G, et al. Comparison of Microbiota in Patients Treated by Surgery or Chemotherapy by 16S rRNA Sequencing Reveals Potential Biomarkers for Colorectal Cancer Therapy. *Front Microbiol.* 2018 Jul 17;9:1607.
91. Komatsu S, Sakamoto E, Norimizu S, et al. Efficacy of perioperative synbiotics treatment for the prevention of surgical site infection after laparoscopic colorectal surgery: a randomized controlled trial. *Surg Today.* 2016 Apr;46(4):479-90.
92. Wang F, Meng J, Zhang L, et al. Morphine induces changes in the gut microbiome and metabolome in a morphine dependence model. *Sci Rep.* 2018 Feb 26;8(1):3596.
93. Demehri FR, Barrett M, Teitelbaum DH. Changes to the Intestinal Microbiome With Parenteral Nutrition: Review of a Murine Model and Potential Clinical Implications. *Nutr Clin Pract.* 2015 Dec;30(6):798-806.
94. Lian X, Zhu Q, Sun L, et al. Effect of Anesthesia/Surgery on Gut Microbiota and Fecal Metabolites and Their Relationship With Cognitive Dysfunction. *Front Syst Neurosci.* 2021 Aug 17;15:655695.
95. Huus KE, Ley RE. Blowing Hot and Cold: Body Temperature and the Microbiome. *mSystems.* 2021 Oct 26;6(5):e0070721.



Peritonektomija in HIPEC: sodobne indikacije, preživetje in zapleti

Peritonectomy and HIPEC: Current Indications, Survival and Complications

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IZVLEČEK

Peritonealne metastaze so bile dolgo obravnavane predvsem paliativno, razvoj citoreduktivne kirurgije in hipertermične intraperitonealne kemoterapije pa je pri izbranih bolnikih omogočil kurativno usmerjen lokalno-regionalni pristop.

Uspeh zdravljenja je odvisen predvsem od obsega peritonealne bolezni, ocenjenega s peritonealnim karcinomatозnim indeksom, in od popolnosti citoredukcije. Najbolj prepričljive rezultate smo dosegli pri psevdomiksomu peritoneja, kjer popolna citoredukcija v kombinaciji s hipertermično intraperitonealno kemoterapijo omogoča približno 70–80 % desetletno celokupno preživetje.

ABSTRACT

Peritoneal metastases were long managed mainly with palliative intent, but the development of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy has enabled a potentially curative locoregional approach in selected patients.

Treatment success depends primarily on the extent of peritoneal disease, assessed by the peritoneal carcinomatosis index, and on the completeness of cytoreduction. The most convincing outcomes have been reported in pseudomyxoma peritonei, where complete cytoreduction combined with hyperthermic intraperitoneal chemotherapy can achieve approximately 70–80% 10-year overall survival.

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Pri kolorektalnih peritonealnih metastazah je temelj zdravljenja popolna citoredukcija; raziskava PRODIGE 7 ni dokazala dodatne koristi 30-minutnega oksaliplatinskega protokola hipertermične intraperitonealne kemoterapije. Pri raku želodca je metoda smiselna le pri zelo omejeni peritonealni bolezni, zlasti pri peritonealnem karcinomatoznem indeksu 6 ali manj in izvedljivi popolni citoredukciji. Zaradi pomembne morbiditete mora zdravljenje potekati v visoko specializiranih centrih po multidisciplinarni presoji in z jasno opredeljenim ciljem popolne odstranitve makroskopske bolezni.

In colorectal peritoneal metastases, complete cytoreduction is the cornerstone of treatment; the PRODIGE 7 trial did not demonstrate an additional survival benefit of a 30-minute oxaliplatin-based hyperthermic intraperitoneal chemotherapy protocol. In gastric cancer, this approach is justified only in very limited peritoneal disease, particularly when the peritoneal carcinomatosis index is 6 or lower, and complete cytoreduction is feasible. Because of relevant morbidity, treatment should be performed in highly specialised centres after multidisciplinary assessment and with the clearly defined aim of complete macroscopic disease removal.

UVOD

Peritonealne metastaze pri abdominalnih malignomih pomenijo razsoj bolezni po peritonealni površini. V preteklosti so bile praviloma obravnavane kot znak sistemsko napredovale bolezni, pri kateri je bilo zdravljenje usmerjeno predvsem v paliativno sistemsko kemoterapijo in lajšanje zapletov. Ker je odziv peritonealnih zasevkov na sistemsko zdravljenje pogosto slabši kot pri metastazah v drugih organih, so se razvili lokalno-regionalni pristopi, katerih cilj je odstraniti vidno bolezen in vplivati na mikroskopske ostanke tumorja (1, 2).

Temelj sodobnega pristopa predstavljata CRK in HIPEC. Sugarbaker je s standardizacijo peritonektomijskih postopkov postavil kirurški okvir za zdravljenje peritonealnih malignomov, poznejše raziskave pa so razvijale različne intraperitonealne protokole glede na primarni tumor (3–5). HIPEC se izvaja intraoperativno po predhodni citoredukciji; najpogosteje uporabljeni citostatiki so mitomicin C, oksaliplatin, cisplatin in doksorubicin, perfuzijska tekočina pa je praviloma segreta na 41–43 °C (4, 5).

CRK in HIPEC nista enako koristna pri vseh bolnikih. Razlike med psevdomiksomom peritoneja, kolorektalnim rakom, rakom želodca, GIST in nevroendokrinimi tumorji so velike. Zato je odločanje nujno vezano na biološke značilnosti tumorja, obseg peritonealne bolezni, možnost popolne cito-

redukcije, splošno stanje bolnika in pričakovano perioperativno tveganje. Namen prispevka je povzeti sodobne indikacije za peritonektomijo in HIPEC, primerjati ključne podatke o preživetju in zapletih ter opredeliti, pri katerih bolnikih je tak pristop najbolj utemeljen.

MATERIALI IN METODE

V pregled literature so bili vključeni predvsem klinično pomembni podatki iz randomiziranih raziskav, multicentričnih kohort, sistematičnih pregledov in večjih retrospektivnih analiz, ki obravnavajo citoreduktivno kirurgijo in hipertermično intraperitonealno kemoterapijo pri peritonealnih metastazah abdominalnega izvora. Poudarek je na celokupnem preživetju, preživetju brez ponovitve ali napredovanja bolezni, zapletih in perioperativni smrtnosti.

REZULTATI

Temeljna načela zdravljenja

Peritonealni karcinomatozni indeks in popolnost citoredukcije

PCI je standardizirana metoda ocenjevanja razširjenosti peritonealne bolezni in eden najpomembnejših prognostičnih kazalnikov. Višji PCI praviloma pomeni večjo tumorsko obremenitev, slabšo možnost popolne citoredukcije in slabše preživetje.

Kljub temu PCI sam po sebi ni zadosten, saj je pomembna tudi lokacija zasevkov; prizadetost tankega črevesa, zlasti več segmentov ali distalnega ileuma, lahko onemogoči popolno resekcijo tudi pri zmernem PCI (6, 19, 20).

CC-klasifikacija opisuje popolnost citoredukcije. CC0 pomeni odsotnost makroskopsko vidne bolezni, CC-1 rezidualne noduse manjše od 2,5 mm, CC-2 in CC-3 pa večjo rezidualno bolezen. Pri večini abdominalnih tumorjev je za dolgoročno korist potrebna CC-0 citoredukcija. Pri psevdomiksomu peritoneja je lahko sprejemljiva tudi CC-1 citoredukcija, ker je biologija bolezni manj agresivna (6, 7).

Če nismo dosegli popolne ali skoraj popolne citoredukcije, HIPEC ne more nadomestiti nepopolne kirurgije. To je klinično pomembno, ker se v večini raziskav kot najmočnejši napovedni dejavnik izida pojavlja popolnost citoredukcije, medtem ko je dodatna vrednost HIPEC odvisna od primarnega tumorja, protokola, trajanja perfuzije, izbranega citostatika in predhodne sistemske terapije (10, 14, 21, 23).

Primerjava indikacij in številčnih izidov

V preglednici Tabela 1 so zbrani ključni podatki o preživetju, selekciji bolnikov in kritični oceni metode po posameznih skupinah bolezni.

Posamezne indikacije

Psevdomiksom peritoneja

Psevdomiksom peritoneja je redka peritonealna maligna bolezen, najpogosteje povezana z mucinoznim tumorjem slepiča. V primerjavi z večino drugih peritonealnih metastaz je pogosto omejen in počasi rastoč, zato je agresivno lokalno zdravljenje najbolj utemeljeno prav pri tej bolezni. Pri PMP slepiča je bila popolna CRK (CC-0) v kombinaciji s HIPEC povezana s 5-letnim celotnim preživetjem 85 % in 10-letnim celotnim preživetjem 75 % (7, 48).

Kritično je treba poudariti, da rezultat tudi pri PMP ni odvisen samo od HIPEC, temveč predvsem od popolnosti citoredukcije in histološkega podtipa. Peritonealna mucinozna karcinomatoza ima slabšo prognozo kot difuzna peritonealna adenomucinoza ali hibridne oblike. Če ni mogoče doseči CC-0 ali CC-1, se lahko pri izbranih bolnikih izvede kirurško čim bolj obsežna odstranitev tumorja, vendar so rezultati slabši kot pri popolni citoredukciji (7, 49).

Kolorektalni rak

Kolorektalni rak je ena najpogostejših indikacij za razmislek o CRK in HIPEC. Sinhrono peritonealne metastaze so prisotne pri približno 6–7 % bolnikov s kolorektalnim rakom, skoraj polovica teh bolnikov pa ima peritonej kot edino mesto metastatske bolezni (9–11, 50).

Pri bolnikih, zdravljenih samo paliativno, so peritonealne metastaze kolorektalnega raka povezane s slabšim preživetjem kot metastaze v jetrih ali pljuči: mediano OS je 16,3 meseca pri peritonealnih metastazah, 19,1 meseca pri izoliranih jetrnih metastazah in 24,6 meseca pri izoliranih pljučnih metastazah (13, 51).

Randomizirana raziskava Verwaala in sod. je že leta 2003 pokazala pomembno izboljšanje preživetja pri bolnikih, zdravljenih s CRK in HIPEC, v primerjavi s sistemsko kemoterapijo in paliativno kirurgijo (8). Kasnejše multicentrične analize so poročale o medianem OS okoli 40 mesecev, kadar je bila dosežena makroskopsko popolna resekcija (9, 11, 12).

Najpomembnejša sodobna raziskava za kritično presojo HIPEC pri kolorektalnem raku je PRODIGE 7. V raziskavo je bilo vključenih 265 bolnikov, 133 v skupino CRK + HIPEC in 132 v skupino samo CRK. Vključeni so bili bolniki s PCI ≤ 25 , WHO zmogljivostjo 0 ali 1, normalno jetrno funkcijo in ustrezno hematološko funkcijo. HIPEC je temeljil na oksaliplatinu in je trajal 30 minut. Mediano OS

Tabela 1: Primerjava indikacij, izida zdravljenja in selekcije bolnikov pri peritonektomiji in HIPEC
Table 1: Comparison of indications, treatment outcomes and patient selection for peritonectomy and HIPEC

Bolezen / skupina	Ključni podatki o preživetju	Izbor bolnikov / pragovi	Kritična ocena
Pseudomiksom peritoneja (PMP)	CC-0 + HIPEC ima 5-letno OS 85 % in 10-letno OS 75 %; širše se navaja 10-letno OS približno 70–80 % (7, 48)	Najboljši izidi pri CC-0/CC-1; pomemben je histološki podtip. PMCA ima slabšo prognozo kot DPAM ali hibridni tumorji (7).	CC-0 in CC-1 + HIPEC je zlati standard.
Kolorektalni rak	Pri paliativnem zdravljenju je mediano OS pri peritonealnih metastazah 16,3 meseca; v PRODIGE 7 je bilo OS 41,7 meseca pri CRK + HIPEC in 41,2 meseca pri sami CRK. Petletno je bilo v obeh skupinah približno 15 % bolnikov ocenjenih kot ozdravljenih (10, 13).	Sinhrona peritonealne metastaze so prisotne pri 6–7 % bolnikov s CRC; skoraj polovica jih ima samo peritonealne metastaze. Največja korist je pri nizkem PCI; navedeni pragovi se razlikujejo: PCI ≤ 10, ≤ 12, ≤ 13 ali do 20 (9, 10, 14–18).	CRK je temelj. Dodatek 30-minutnega oksaliplatinskega HIPEC po PRODIGE 7 ni dokazal koristi, zato HIPEC ni primeren pri vseh bolnikih.
Rak želodca	Sistemska zdravljenje pri peritonealnih metastazah običajno doseže OS približno 8–10 mesecev. Pri PCI ≤ 6 in CC-0 so opisane mediane OS nad 40 mesecev; v italijanski multicentrični raziskavi 40,7 meseca pri CC-0 proti 10,7 meseca pri nepopolni resekciji ter 44,3 meseca pri PCI ≤ 6 proti 13,4 meseca pri PCI > 6 (29, 32).	Najprimernejši so bolniki z omejeno peritonealno boleznijo, običajno PCI ≤ 6, brez razširjene sistemske bolezni in z realno možnostjo CC-0 (30–32).	Obetavno, vendar še brez dokončne potrditve v velikih randomiziranih raziskavah. Ne sme se uporabljati rutinsko pri obsežni bolezni.
GIST	Pred imatinibom je bilo preživetje pri metastatskem GIST 10–20 mesecev, 5-letno OS manj kot 10 % (44). Pri bolnikih z odgovorom ali stabilno boleznijo po imatinibu je bilo v španski retrospektivni primerjavi OS 87,6 meseca z imatinibom + CRK proti 59,9 meseca z imatinibom brez operacije (34).	Operacija je smiselna predvsem pri odgovoru ali stabilni bolezni po TKI; ne prej kot po 6 mesecih in praviloma ne pozneje kot po 2 letih od začetka TKI (45–47).	CRK ima lahko vlogo pri izbranih bolnikih, HIPEC pa nima jasno opredeljene vloge.
GEP-NET	Izid močno določata jetrna prizadetost in gradus tumorja (43).	Popolna resekcija je priporočena, kadar je izvedljiva. Tudi delna ima lahko korist, če se odstrani vsaj 70 % tumorske mase (40–42).	Vloga HIPEC ostaja pod vprašajem.

Legenda: DPAM: diseminirana peritonealna adenomucinoza, PMCA: peritonealna mucinozna karcinomatoza, TKI: inhibitor tirozinskih kinaz, GIST: gastrointestinalni stromalni tumorji, GEP-NET: gastroenteropankreatični nevroendokrini tumorji

je bilo 41,7 meseca v skupini CRK + HIPEC in 41,2 meseca v skupini samo CRK ($p = 0,99$). Preživetje brez ponovitve se ni pomembno razlikovalo, pet let po zdravljenju pa je bilo približno 15 % bolnikov v obeh skupinah ocenjenih kot ozdravljenih (8, 10).

Ti podatki kažejo, da je pri kolorektalnih peritonealnih metastazah temelj zdravljenja popolna CRK. Dodatek oksaliplatinskega HIPEC ni izboljšal preživetja, hkrati pa je bila 60-dnevna stopnja zapletov stopnje 3 ali več višja v skupini CRK + HIPEC kot v skupini samo CRK (26 % proti 15 %, $p = 0,035$).

Na 30. dan razlika ni bila statistično značilna, vendar je bilo zapletov stopnje 3 ali več numerično več pri CRK + HIPEC (42 % proti 32 %) (8, 10).

Kritična razlaga PRODIGE 7 ni, da je HIPEC pri kolorektalnem raku dokončno brez vrednosti, temveč da 30-minutni oksaliplatinski protokol po popolni CRK ni dokazal dodatne koristi. Pomembne omejitve so kratko trajanje perfuzije, predhodna izpostavljenost bolnikov oksaliplatinu in možnost rezistence ter neenotnost optimalnega HIPEC protokola. Odziv na lokalni oksaliplatin je lahko povezan s trajanjem izpostavljenosti, zato ostaja vprašanje drugačnih protokolov, na primer daljše perfuzije ali mitomicina C, odprto (23–25).

Tudi prag PCI ostaja predmet razprav. Različni avtorji so navajali največjo korist pri $PCI \leq 10$, drugi pri $PCI \leq 12$ ali ≤ 13 , nekateri pa kot zgornjo mejo navajajo PCI 20. Bolniki s $PCI > 20$ praviloma niso dobri kandidati za CRK z ali brez HIPEC, saj je preživetje slabše in verjetnost popolne citoredukcije manjša. Poleg številčne vrednosti PCI je treba oceniti tudi prizadetost tankega črevesa in število prizadetih regij (12, 14–20).

Profilaktični HIPEC pri visokorizičnem kolorektalnem raku za zdaj nima dovolj podpore za rutinsko uporabo. PROPHYLOCHIP-PRODIGE 15 ni pokazal statistično značilne razlike v triletnem preživetju brez bolezni (DFS) med drugo operacijo z HIPEC in opazovanjem (44 % proti 53 %, $p = 0,82$). Podobno COLOPEC ni pokazal statistično značilne razlike v 18-mesečnem peritonealnem DFS med adjuvantnim HIPEC in standardnim zdravljenjem (80,9 % proti 76,2 %, $p = 0,28$) (26–27).

Rak želodca

Peritonealne metastaze pri raku želodca so pogoste in prognozično neugodne. Prisotne so pri približno 17 % novo diagnosticiranih bolnikov, pri stadiju III pa se lahko pojavijo do 40 % primerov. Pri sistemskem zdravljenju je mediano OS običajno približno 8–10 mesecev (28, 52, 53).

Pri skrbno izbranih bolnikih z omejeno peritonealno boleznijo so rezultati bistveno boljši. V francoski multicentrični raziskavi 159 bolnikov je bila popolna citoredukcija neodvisno povezana z daljšim preživetjem: mediano OS po CC-0 je bilo 15 mesecev, v celotni skupini pa 9,2 meseca; petletno OS po CC-0 je bilo 23 % (28, 29).

Najbolj izrazita korist je opisana pri nizkem PCI. Yonemura in sod. so pri 95 bolnikih pokazali, da je bil CC-0 dosežen pri 91 % bolnikov s $PCI \leq 6$, vendar samo pri 42 % bolnikov s $PCI \geq 7$ (28). Italijanska multicentrična raziskava pri sinhronih peritonealnih metastazah želodčnega raka je poročala o medianem OS 40,7 meseca po popolni citoredukciji proti 10,7 meseca po nepopolni resekciji ($p = 0,003$). Pri $PCI \leq 6$ je bilo mediano OS 44,3 meseca, pri $PCI > 6$ pa 13,4 meseca ($p = 0,005$) (32).

CYTO-CHIP, največja opazovalna študija na tem področju, je vključila 277 bolnikov iz 19 francoskih centrov. Pokazala je boljše OS in DFS pri CRK + HIPEC v primerjavi s samo CRK, brez pomembnega povečanja večje morbiditete in 90-dnevne smrtnosti. Vendar gre za opazovalno študijo z analizo prilagajanja na verjetnost izbire zdravljenja, zato ne predstavlja dokončne potrditve randomiziranih raziskav. Zato je treba zdravljenje omejiti na skrbno izbrane bolnike v izkušenih centrih (30).

Pri raku želodca je zato CRK + HIPEC utemeljen predvsem pri bolnikih z zelo omejeno peritonealno boleznijo, pričakovano CC-0 citoredukcijo, dobrim splošnim stanjem in ustreznim odgovorom na sistemsko zdravljenje. Pri obsežnem PCI, neodzivu na sistemsko zdravljenje ali agresivni biologiji tumorja je tveganje, da poseg povzroči veliko morbiditeto brez realne onkološke koristi, visoko (30–32).

Manj pogoste indikacije

Pri GIST je ključna sistemska tarčna terapija z imatinibom. Operacija ima lahko vlogo pri bolnikih z odgovorom ali stabilno boleznijo po TKI (45–47). V španski retrospektivni primerjavi je bilo mediano

OS 87,6 meseca pri kombinaciji imatiniba in CRK proti 59,9 meseca pri imatinibu brez operacije. HIPEC pri GIST nima jasno dokazane vloge (34).

Pri gastroenteropankreatičnih nevroendokrinih tumorjih (GEP-NET) so peritonealne metastaze prisotne pri približno 20 % bolnikov. Kirurška resekcija je smiselna, kadar je popolna resekcija izvedljiva; kadar ni, lahko nepopolna citoredukcija koristi, če je mogoče odstraniti vsaj 70 % tumorske mase. Vloga HIPEC ostaja pod vprašajem (35–36, 38–41).

Zapleti, tveganja in organizacijske zahteve

CRK + HIPEC je obsežen kirurško-onkološki poseg, zato so zapleti pričakovani in klinično pomembni. Najpogostejši zapleti vključujejo krvavitve, anastomotsko puščanje, intraabdominalne abscese, okužbe, ileus, respiratorne zaplete ter hemato-, hepato- in nefrotoksičnost, odvisno od uporabljenega citostatika. Posebej pri cisplatinških protokolih je opisana akutna ledvična okvara, tveganje pa narašča z obsegom operacije (4, 21, 37).

S povečanjem izkušenj in razvojem specializiranih centrov sta se morbiditeta in smrtnost zmanjšali ter postali primerljivi z drugimi velikimi gastrointestinalnimi onkološkimi operacijami. Kljub temu je francoska analiza 5562 bolnikov pokazala, da bi bilo več kot polovico pooperativnih smrti po CRK in HIPEC mogoče preprečiti. Ta podatek je pomemben, ker kaže, da uspeh metode ni odvisen samo od indikacije, temveč tudi od organizacije in izkušenj centra (21, 22).

V PRODIGE 7 je bila 30-dnevna stopnja zapletov stopnje 3 ali več 42 % pri CRK + HIPEC in 32 % pri sami CRK, brez statistično značilne razlike. Do 60. dne pa je bila razlika značilna: 26 % pri CRK + HIPEC proti 15 % pri CRK ($p = 0,035$). To potrjuje, da se pri HIPEC zapleti lahko pojavijo tudi kasneje in lahko odložijo nadaljevanje sistemskega zdravljenja (8, 10).

RAZPRAVA

CRK + HIPEC je ena najbolj intenzivnih oblik zdravljenja peritonealnih malignomov. Njena prednost je logična: peritonealna bolezen je lahko lokalno-regionalno omejena, sistemska terapija pa ima v peritoneju omejeno učinkovitost. Kljub temu se je treba izogniti nekritičnemu razumevanju HIPEC kot univerzalnega dodatka k kirurgiji. Dokazi kažejo, da je pri večini tumorjev najpomembnejši dejavnik popolna citoredukcija, medtem ko je dodatna vrednost HIPEC odvisna od histologije, protokola, trajanja perfuzije, izbranega citostatika in predhodnega sistemskega zdravljenja (10, 23–25).

Najboljši dokaz za to je kolorektalni rak. PRODIGE 7 je dokazal, da lahko popolna CRK doseže mediano OS nad 40 mesecev, kar je bistveno bolje od paliativnih rezultatov. Hkrati pa dodatek 30-minutnega oksaliplatinskega HIPEC ni izboljšal OS. Zato bi bilo napačno trditi, da je raziskava ovrgla CRK; dejansko je potrdila njen pomen. Prav tako bi bilo preveč poenostavljeno trditi, da je dokončno ovrgla vse oblike HIPEC; bolj pravilna interpretacija je, da ni dokazala koristi konkretnega oksaliplatinskega protokola v izbranem kliničnem kontekstu (10, 23).

Pri raku želodca so podatki bolj obetavni, vendar manj trdni. Razlike v preživetju pri PCI ≤ 6 in CC-0 so velike, vendar večinoma izhajajo iz retrospektivnih ali opazovalnih raziskav. Zato je treba CRK + HIPEC pri raku želodca razumeti kot možnost za zelo ozko skupino bolnikov, ne pa kot rutinski standard. Pri obsežnem PCI, neugodnem biološkem poteku, neodzivu na sistemsko zdravljenje ali nezmožnosti CC-0 je tveganje, da poseg povzroči veliko morbiditeto brez realne onkološke koristi (30, 32).

Pri PMP je položaj drugačen, ker je biologija bolezni pogosto bolj omejena in počasnejša. Zato je CRK + HIPEC najmočnejše utemeljena prav pri PMP, kjer so 10-letna preživetja 70–80 % bistveno boljše kot pri večini drugih peritonealnih malignomov (7).

Pri manj pogostih prebavnih tumorjih je treba biti še posebej previden. Pri GIST in GEP-NET je vloga sistemskega oziroma biološkega zdravljenja pogosto pomembnejša od HIPEC, operacija pa mora biti strogo individualizirana (34–36).

CRK z ali brez HIPEC naj se izvaja izključno v visoko specializiranih centrih za peritonealne malignome, kjer so na voljo izkušen abdominalni onkološki kirurg, anesteziološka ekipa, internistični onkolog, radiolog, patolog, intenzivna terapija, perioperativna prehranska podpora in strukturirano spremljanje zapletov. Obseg posega in možnost zapletov zahtevata center z zadostnim letnim obsegom primerov in jasno oblikovanim multidisciplinarnim konzilijem (21, 22).

Zdravljenje je smiselno pri bolnikih z omejeno peritonealno boleznijo, dobrim splošnim stanjem, brez nenadzorovane ekstraperitonealne bolezni in z realno možnostjo doseganja CC-0 oziroma pri PMP vsaj CC-1. Pri kolorektalnem raku je CRK temelj pri nizkem PCI; dodatek HIPEC naj bo selektiven. Pri raku želodca naj se o CRK + HIPEC razmišlja predvsem pri $PCI \leq 6$ in pričakovani CC-0. Pri PMP je CRK + HIPEC zlati standard, če je bolnik operabilen in je popolna ali skoraj popolna citoredukcija izvedljiva (7, 10, 14, 30–32).

Odločitev moramo sprejeti na multidisciplinarnem konziliju po natančni radiološki oceni, oceni PCI, presoji biologije tumorja, odgovora na sistemsko zdravljenje in operabilnosti. Bolnika je treba pred posegom jasno sezniniti, da je korist odvisna predvsem od možnosti popolne citoredukcije in da HIPEC ni zagotovilo za ozdravitev. Po posegu je potrebno strukturirano pooperativno spremljanje, zgodnje prepoznavanje zapletov in pravočasno nadaljevanje indiciranega sistemskega zdravljenja.

ZAKLJUČEK

CRK in HIPEC sta pomembno spremenila zdravljenje izbranih bolnikov s peritonealnimi malignomi, vendar nista primerni za vse bolnike s peritonealnimi metastazami. Najmočnejša indikacija ostaja psevdomiksom peritoneja, kjer CRK + HIPEC dosega 10-letno celokupno preživetje približno 70–80 %. Pri kolorektalnem raku je popolna CRK ključna, dodatek oksaliplatinskega HIPEC po PRODIGE 7 pa ni izboljšal preživetja. Pri raku želodca je metoda smiselna samo pri zelo izbranih bolnikih, zlasti pri $PCI \leq 6$ in izvedljivi CC-0 citoredukciji.

Zdravljenje mora potekati v specializiranih centrih, po multidisciplinarni presoji in z jasno opredeljenim ciljem, in sicer popolna odstranitev makroskopske bolezni. Kadar popolna citoredukcija ni realno dosegljiva, je korist agresivnega pristopa vprašljiva, tveganje zapletov pa visoko. Kritična uporaba metode pomeni, da CRK z ali brez HIPEC uporabimo takrat, ko ima bolnik zaradi biologije tumorja, omejenega PCI in operabilnosti realno možnost dolgoročnega preživetja, ne pa zgolj zato, ker so peritonealne metastaze prisotne.

Reference

1. Neuwirth MG, Alexander HR, Karakousis GC. Then and now: cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC), a historical perspective. *J Gastrointest Oncol* 2016;7(1):18-28.
2. Sánchez-Hidalgo JM, Rodríguez-Ortiz L, Arjona-Sánchez Á, et al. Colorectal peritoneal metastases: optimal management review. *World J Gastroenterol* 2019;25(27):3484-3502.
3. Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995;221(1):29-42.
4. Glehen O, Cotte E, Kusamura S, et al. Hyperthermic intraperitoneal chemotherapy: nomenclature and modalities of perfusion. *J Surg Oncol* 2008;98(4):242-246.
5. Elias D, Antoun S, Goharin A, et al. Research on the best chemohyperthermia technique of treatment of peritoneal carcinomatosis after complete resection. *Int J Surg Investig* 2000;1(5):431-439.
6. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res* 1996;82:359-374.
7. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Clin Oncol* 2012;30(20):2449-2456.
8. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003;21(20):3737-3743.
9. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol* 2010;28(1):63-68.
10. Quénet F, Elias D, Roca L, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22(2):256-266.
11. Glehen O, Kwiakowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* 2004;22(16):3284-3292.
12. Goéré D, Malka D, Tzanis D, et al. Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? *Ann Surg* 2013;257(6):1065-1071.
13. Franko J, Shi Q, Meyers JP, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the ARCAD database. *Lancet Oncol* 2016;17(12):1709-1719.
14. Turaga K, Levine E, Barone R, et al. Consensus guidelines from the American Society of Peritoneal Surface Malignancies on standardizing the delivery of HIPEC in colorectal cancer patients in the United States. *Ann Surg Oncol* 2014;21(5):1501-1505.
15. Yan TD, Chu F, Links M, et al. Cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma: non-mucinous tumour associated with an improved survival. *Eur J Surg Oncol* 2006;32(10):1119-1124.
16. da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. *J Am Coll Surg* 2006;203(6):878-886.
17. Cavaliere F, De Simone M, Virzi S, et al. Prognostic factors and oncologic outcome in 146 patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery combined with HIPEC: Italian multicenter study S.I.T.I.L.O. *Eur J Surg Oncol* 2011;37(2):148-154.
18. Van Sweringen HL, Hanseman DJ, Ahmad SA, et al. Predictors of survival in patients with high-grade peritoneal metastases undergoing cytoreductive surgery and HIPEC. *Surgery* 2012;152(4):617-625.
19. Benizri EL, Bernard JL, Rahili A, et al. Small bowel involvement is a prognostic factor in colorectal carcinomatosis treated with complete cytoreductive surgery plus HIPEC. *World J Surg Oncol* 2012;10:56.
20. Elias D, Mariani A, Cloutier AS, et al. Modified selection criteria for complete cytoreductive surgery plus HIPEC based on PCI and small bowel involvement for peritoneal carcinomatosis of colorectal origin. *Eur J Surg Oncol* 2014;40(11):1467-1473.
21. Chua TC, Yan TD, Saxena A, et al. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and HIPEC still be regarded as a highly morbid procedure? *Ann Surg* 2009;249(6):900-907.
22. Houzé-Laroye C, Glehen O, Sgarbura O, et al. Half of postoperative deaths after cytoreductive surgery and HIPEC could be preventable: a French root cause analysis on 5562 patients. *Ann Surg* 2021;274(5):797-804.
23. Cashin P, Sugarbaker PH. Hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal and appendiceal peritoneal metastases: lessons learned from PRODIGE 7. *J Gastrointest Oncol* 2021;12(Suppl 1):S120-S128.
24. Kirstein MN, Root SA, Moore MM, et al. Exposure-response relationships for oxaliplatin-treated colon cancer cells. *Anticancer Drugs* 2008;19(1):37-44.
25. Lemoine L, Thijssen E, Carleer R, et al. Body surface area-based vs concentration-based perioperative intraperitoneal chemotherapy after optimal cytoreductive surgery in colorectal peritoneal surface malignancy treatment: COBOX trial. *J Surg Oncol* 2019;119(8):999-10010.
26. Goéré D, Glehen O, Quenet F, et al. Second-look surgery plus HIPEC versus surveillance in patients at high risk of developing colorectal peritoneal metastases (PROPHYLOCHIP-PRODIGE 15): a randomised, phase 3 study. *Lancet Oncol* 2020;21(9):1147-1154.
27. Klaver CEL, Wisselink DD, Punt CJA, et al. Adjuvant HIPEC in patients with locally advanced colon cancer (COLOPEC): a multicentre, open-label, randomised trial. *Lancet Gastroenterol Hepatol* 2019;4(10):761-770.
28. Yonemura Y, Elnemr A, Endou Y, et al. Multidisciplinary therapy for treatment of patients with peritoneal carcinomatosis from gastric cancer. *World J Gastrointest Oncol* 2010;2(2):85-97.
29. Glehen O, Gilly FN, Arvieux C, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. *Ann Surg Oncol* 2010;17(9):2370-2377.
30. Bonnot PE, Piessen G, Kepenekian V, et al. Cytoreductive surgery with or without HIPEC for gastric cancer with peritoneal metastases (CYTO-CHIP study): a propensity score analysis. *J Clin Oncol* 2019;37(23):2028-2040.
31. Coccolini F, Catena F, Glehen O, et al. Complete versus incomplete cytoreduction in peritoneal carcinosis from gastric cancer, with consideration to PCI cut-off: systematic review and meta-analysis. *Eur J Surg Oncol* 2015;41(7):911-919.
32. Marano L, Marrelli D, Sammartino P, et al. Cytoreductive surgery and HIPEC for gastric cancer with synchronous peritoneal metastases: multicenter study of Italian Peritoneal Surface Malignancies Oncoteam-S.I.C.O. *Ann Surg Oncol* 2021;28(13):9060-9070.

33. Canbay E, Mizumoto A, Ichinose M, et al. Outcome data of patients with peritoneal carcinomatosis from gastric origin treated by bidirectional chemotherapy prior to cytoreductive surgery and HIPEC in a single specialized center in Japan. *Ann Surg Oncol* 2014;21(4):1147-1152.
34. Rubió-Casadevall J, Martínez-Trufero J, García-Albeniz X, et al. Role of surgery in patients with recurrent, metastatic, or unresectable locally advanced gastrointestinal stromal tumors sensitive to imatinib: retrospective analysis of GEIS. *Ann Surg Oncol* 2015;22(9):2948-2957.
35. Kianmanesh R, Ruzsniwski P, Rindi G, et al. ENETS consensus guidelines for the management of peritoneal carcinomatosis from neuroendocrine tumors. *Neuroendocrinology* 2010;91(4):333-340.
36. Benhaim L, Faron M, Hadoux J, et al. Long-term results after surgical resection of peritoneal metastasis from neuroendocrine tumors. *Neuroendocrinology* 2021;111(6):599-608.
37. Liesenfeld LF, Quiring E, AlSaeedi M, et al. Extensive peritonectomy is an independent risk factor for cisplatin HIPEC-induced acute kidney injury. *Ann Surg Oncol* 2023;30(5):2646-2656.
38. Chicago Consensus Working Group. The Chicago consensus on peritoneal surface malignancies: management of neuroendocrine tumors. *Ann Surg Oncol* 2020;27(6):1788-1792.
39. Chicago Consensus Working Group. The Chicago consensus on peritoneal surface malignancies: management of neuroendocrine tumors. *Cancer* 2020;126(11):2561-2565.
40. Wonn SM, Limbach KE, Pommier SJ, et al. Outcomes of cytoreductive operations for peritoneal carcinomatosis with or without liver cytoreduction in patients with small bowel neuroendocrine tumors. *Surgery* 2021;169(1):168-174.
41. Woltering EA, Voros BA, Beyer DT, et al. Aggressive surgical approach to the management of neuroendocrine tumors: a report of 1,000 surgical cytoreductions by a single institution. *J Am Coll Surg* 2017;224(4):434-447.
42. Maxwell JE, Sherman SK, O'Dorisio TM, et al. Liver-directed surgery of neuroendocrine metastases: what is the optimal strategy? *Surgery* 2016;159(1):320-333.
43. Tomassetti P, Campana D, Piscitelli L, et al. Endocrine tumors of the ileum: factors correlated with survival. *Neuroendocrinology* 2006;83(5-6):380-386.
44. Tielen R, Verhoef C, van Coevorden F, et al. Surgery after treatment with imatinib and/or sunitinib in patients with metastasized gastrointestinal stromal tumors: is it worthwhile? *World J Surg Oncol* 2012;10:111.
45. Bonvalot S, Eldweny H, Péchoux CL, et al. Impact of surgery on advanced gastrointestinal stromal tumors (GIST) in the imatinib era. *Ann Surg Oncol* 2006;13(12):1596-1603.
46. Mussi C, Ronellenfitch U, Jakob J, et al. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients?. *Ann Oncol* 2010;21(2):403-408.
47. Sym SJ, Ryu MH, Lee JL, et al. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). *J Surg Oncol* 2008;98(1):27-33.
48. Govaerts K, Lurvink RJ, De Hingh IHJT, et al. Appendiceal tumours and pseudomyxoma peritonei: literature review with PSOGI/EURACAN clinical practice guidelines for diagnosis and treatment. *Eur J Surg Oncol* 2021;47(1):11-35.
49. Moran BJ, Tzivanakis A. The concept of "obstruction-free survival" as an outcome measure in advanced colorectal cancer management. *Pleura Peritoneum* 2018;3(1):20180101.
50. Alexandrescu ST, Anastase DT, Grigorie RT, et al. Influence of the primary tumor location on the pattern of synchronous metastatic spread in patients with stage IV colorectal carcinoma, according to the 8th edition of the AJCC Staging System. *J Gastrointest Liver Dis* 2020;29(4):561-568.
51. Rosa F, Galiandro F, Ricci R, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal peritoneal metastases: analysis of short- and long-term outcomes. *Langenbecks Arch Surg* 2021;406(8):2797-2805.
52. Gretscher S, Siegel R, Estévez-Schwarz L, et al. Surgical strategies for gastric cancer with synchronous peritoneal carcinomatosis. *Br J Surg* 2006;93(12):1530-1535.
53. Roviello F, Caruso S, Neri A, et al. Treatment and prevention of peritoneal carcinomatosis from gastric cancer by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: overview and rationale. *Eur J Surg Oncol* 2013;39(12):1309-1316.



Metabolic and Intestinal Complications Following Urinary Intestinal Diversion: Mechanisms, Clinical Impact, and Management

Metabolni in intestinalni zapleti po derivaciji urina: mehanizmi, klinični pomen in zdravljenje

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Keywords: Hyperchloremic metabolic acidosis; small intestinal bacterial overgrowth; vitamin B12 deficiency; chronic kidney disease; osteoporosis.

ABSTRACT

Urinary intestinal diversion is an essential reconstructive procedure after radical cystectomy and in selected patients with complex lower urinary tract disorders. Incorporation of bowel segments into the urinary tract may cause metabolic, renal, nutritional, and gastrointestinal complications that require lifelong surveillance.

This narrative review summarises current evidence on the mechanisms, clinical impact, diagnosis, and long-term management of these complications. We performed structured PubMed/MEDLINE search. Publications focused primarily on toxicity attributable to neoadjuvant or adjuvant chemotherapy or pelvic

POVZETEK

Urinarna črevesna preusmeritev je pomemben rekonstruktivni poseg po radikalni cistektomiji in pri izbranih bolnikih s kompleksnimi boleznimi spodnjih sečil. Vključitev črevesnega segmenta v sečila lahko povzroči presnovne, ledvične, prehranske in gastrointestinalne zaplete, ki zahtevajo vseživljenjsko spremljanje.

Namen preglednega članka je povzeti sodobne dokaze o patofizioloških mehanizmih, kliničnem pomenu, diagnostiki in dolgoročni obravnavi teh zapletov. Izvedli smo strukturirano iskanje v zbirki PubMed/MEDLINE.

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radiotherapy were excluded when diversion-specific outcomes could not be separated.

Chronic hyperchloremic metabolic acidosis is a central mechanism linking electrolyte disturbances, renal dysfunction, and skeletal demineralisation. Chronic diarrhoea, malabsorption, vitamin B12 deficiency, and small intestinal bacterial overgrowth (SIBO) may further compromise nutritional status. In symptomatic patients, assess SIBO with standardised hydrogen-methane breath testing or, in selected cases, small-bowel aspirate culture; treat confirmed symptomatic disease while correcting underlying anatomical, motility, and nutritional factors. Chronic liver disease and sex-specific endocrine or functional consequences require individualised preoperative assessment and follow-up. Long-term outcomes depend on structured, risk-adapted, multidisciplinary surveillance of renal function, acid-base status, nutritional parameters, bone health, gastrointestinal symptoms, and selected endocrine outcomes.

INTRODUCTION

Urinary intestinal diversion (UD) is a fundamental component of reconstructive urologic surgery. It is most commonly performed after radical cystectomy (RC) for muscle-invasive bladder cancer, but it may also be required during anterior or total pelvic exenteration for selected locally advanced or recurrent pelvic malignancies and, less frequently, for complex benign lower urinary tract disorders. Therefore, consider the indication for surgery, prior pelvic treatment, comorbidity burden, and anticipated bowel and renal reserve when selecting the diversion technique (1–4).

Depending on patient characteristics and surgical indications, reconstruction may use incontinent techniques, such as an ileal conduit, or continent diversions, including orthotopic neobladders and continent cutaneous reservoirs. Although these procedures improve urinary function and quality of

Raziskave, osredotočene predvsem na toksičnost neoadjuvantne ali adjuvantne kemoterapije oziroma medeničnega obsevanja, so bile izključene, kadar njihovih učinkov ni bilo mogoče ločiti od posledic same urinske derivacije. Kronična hiperkloremična presnovna acidoza je osrednji mehanizem elektrolitskih motenj, napredovanja ledvične okvare in izgube kostne mase.

Kronična driska, malabsorpcija in prekomerna razrast bakterij v tankem črevesu (SIBO) lahko dodatno poslabšajo prehranski status. Pri simptomatskih bolnikih je priporočljivo objektivno testiranje za SIBO, potrjene primere pa je treba zdraviti ob sočasni odpravi osnovnega vzroka in prehranskih pomanjkljivosti.

Posebno oceno potrebujejo bolniki s kronično jetrno boleznijo ter bolniki s funkcionalnimi ali hormonskimi posledicami operacije. Dobri dolgoročni rezultati so odvisni od strukturiranega, tveganju prilagojenega in multidisciplinarnega spremljanja.

life, they expose patients to a distinct spectrum of long-term metabolic, renal, gastrointestinal, nutritional, and functional complications that require lifelong surveillance (1–3).

The pathophysiological basis of many complications is the continued absorptive and secretory activity of the intestinal mucosa after incorporation into the urinary tract. Exposure of ileal or colonic segments to urine promotes exchange of chloride, ammonium, bicarbonate, and other solutes across the bowel wall. The magnitude of these changes depends on the bowel segment and length used, urine-bowel contact time, baseline kidney function, hydration, and follow-up duration (1, 5).

Bowel resection and functional exclusion may also disrupt bile acid recycling, intestinal transit, nutrient absorption, and the gut microbial environment. Patients may consequently develop chronic diarrhoea, malabsorption, vitamin and micronu-

trient deficiencies, and SIBO. These manifestations can reduce quality of life even when the urinary functions satisfactorily (2, 3, 6, 7).

Long-term complications often develop gradually and may remain clinically silent until organ dysfunction is advanced. Symptom-driven assessment alone is therefore insufficient. Contemporary guidance supports structured functional follow-up that includes renal function, acid-base balance, vitamin B12 status, upper urinary tract assessment, and evaluation of patient-reported functional outcomes (4, 8).

Functional outcomes differ by sex and by the extent of organ and nerve preservation. Men may experience erectile, orgasmic, or ejaculatory dysfunction and daytime or nocturnal incontinence. Women may develop impaired neobladder emptying requiring clean intermittent catheterisation, incontinence, pelvic organ prolapse, dyspareunia, or vaginal stenosis. These outcomes justify sex-specific assessment of urinary, sexual, and quality-of-life domains during long-term follow-up (4).

Endocrine consequences require separate consideration when RC or pelvic exenteration includes bilateral salpingo-oophorectomy, causes premature loss of ovarian function, or is followed by persistent symptomatic hypogonadism in men. Menopausal hormone therapy and testosterone replacement are not routine treatments for every patient after UD; they should be considered only after confirmation of the relevant endocrine condition, assessment of oncologic and cardiovascular contraindications, and shared decision-making (9, 10).

The present review focuses on diversion-related metabolic and intestinal consequences. Oncologic outcomes and toxicities primarily attributable to systemic anticancer treatment or pelvic radiotherapy are outside its scope, although these exposures remain clinically relevant when interpreting an individual patient's postoperative risk.

This literature review summarises current evidence on metabolic, renal, intestinal, nutritional, skeletal, hepatic, and selected endocrine consequences associated with urinary intestinal diversion, with particular emphasis on pathophysiological mechanisms, clinical significance, diagnostic evaluation, and risk-adapted long-term management.

LITERATURE SEARCH AND NARRATIVE SYNTHESIS

We conducted narrative literature search was conducted in PubMed/MEDLINE to identify publications addressing metabolic and intestinal complications associated with urinary intestinal diversion. Medical Subject Headings (MeSH) and free-text terms included urinary diversion, ileal conduit, orthotopic neobladder, metabolic acidosis, electrolyte imbalance, renal function, chronic kidney disease, ureteroenteric stricture, small intestinal bacterial overgrowth, malabsorption, vitamin B12 deficiency, anaemia, osteoporosis, cirrhosis, chronic liver disease, surgical menopause, hormone therapy, hypogonadism, and testosterone replacement therapy. Boolean operators (AND and OR) were used to combine terms.

We prioritised adult studies, clinical guidelines, systematic and narrative reviews, and original research addressing metabolic, renal, gastrointestinal, nutritional, skeletal, hepatic, or functional outcomes after urinary intestinal diversion. We excluded paediatric studies, case reports, conference abstracts without full manuscripts, and publications unrelated to diversion-associated consequences. We excluded publications focused primarily on neoadjuvant or adjuvant chemotherapy or pelvic radiotherapy when diversion-specific outcomes could not be separated.

Because of substantial heterogeneity in study design, patient populations, diversion techniques, follow-up duration, and reported outcomes, we synthesised the evidence narratively and organised it into thematic sections. This article is a narrative review and does not constitute a systematic review or meta-analysis.

METABOLIC AND INTESTINAL COMPLICATIONS

Acid-Base and Electrolyte Disturbances

Metabolic acid–base abnormalities are among the best documented long-term complications of urinary intestinal diversion. Their development is primarily related to the persistent exposure of bowel mucosa to urine, which allows continuous exchange of electrolytes and solutes across the intestinal epithelium. Ileal and colonic segments retain their absorptive and secretory functions after reconstruction, promoting chloride and ammonium absorption together with bicarbonate secretion into the intestinal lumen. This process predisposes patients to hyperchloremic metabolic acidosis, particularly when large bowel segments are incorporated into the urinary tract or when renal function is impaired (1, 5).

The severity of metabolic acidosis varies according to the type of diversion, the length of bowel used, baseline kidney function, and duration of postoperative follow-up. In most patients, the disturbance remains mild, but persistent acid retention may contribute to fatigue, reduced exercise tolerance, muscle weakness, and progressive deterioration of mineral metabolism. Patients with chronic kidney disease have diminished capacity to compensate for the increased acid load and are therefore at substantially greater risk of clinically significant biochemical abnormalities (1).

Electrolyte disturbances frequently accompany acid–base imbalance. Hypokalemia may occur secondary to gastrointestinal and renal potassium losses, whereas alterations in sodium and chloride concentrations reflect ongoing ion exchange between urine and intestinal mucosa. Although severe electrolyte disorders are uncommon in patients with preserved renal function, regular laboratory surveillance is recommended because abnormalities may develop gradually and remain asymptomatic for prolonged periods (1, 2).

The choice of bowel segment also influences metabolic risk. Colonic urinary diversions generally pro-

duce greater chloride absorption and bicarbonate loss than ileal reconstructions, increasing the likelihood of clinically relevant acidosis. Conversely, shorter ileal conduits tend to produce fewer metabolic consequences than continent reservoirs or orthotopic neobladders constructed from longer bowel segments, although long-term monitoring remains necessary regardless of diversion type (3, 11).

Taken together, current evidence indicates that hyperchloremic metabolic acidosis is the central metabolic disturbance after urinary intestinal diversion and provides a pathophysiological basis for several renal, nutritional, muscular, and skeletal sequelae. Periodic assessment of serum bicarbonate, electrolytes, and renal function is therefore an essential for follow-up (1, 5). Table 1 summarises the principal complication categories.

Renal and Urinary Tract Complications

Renal impairment is one of the most important long-term concerns after urinary intestinal diversion. Deterioration is usually multifactorial and may reflect chronic acid load, recurrent infection, urinary obstruction, ureteroenteric stricture, nephrolithiasis, dehydration, and pre-existing chronic kidney disease. A longer bowel segment and prolonged urine–bowel contact may increase metabolic burden, whereas obstruction and infection can cause potentially preventable structural loss of renal function (1, 4, 8, 11).

Baseline renal function strongly modifies postoperative risk. Patients with reduced glomerular filtration rate have less capacity to excrete the additional acid load and are more susceptible to persistent metabolic acidosis and progressive kidney dysfunction. Even patients with preserved renal reserve require surveillance because clinically important abnormalities may emerge years after surgery (1, 4, 8).

The type of diversion also influences renal outcomes. Ureteroenteric obstruction, recurrent pyelonephritis, upper urinary tract dilatation, and morphological renal changes occur after both incontinent

Table 1. Comparative overview of metabolic and intestinal complications after urinary intestinal diversion

Complication category	Main mechanisms	Clinical manifestations	Key findings	Supporting references
Acid–base disturbances	Chloride and ammonium absorption, bicarbonate loss	Fatigue, weakness, asymptomatic acidosis	Hyperchloremic metabolic acidosis is the central metabolic disturbance after urinary intestinal diversion	Sperling et al. (1); Hautmann (5)
Electrolyte abnormalities	Intestinal ion exchange and renal compensation	Hypokalemia, altered chloride and bicarbonate levels	Electrolyte abnormalities often accompany chronic acid–base disturbance	Sperling et al. (1)
Renal complications	Chronic acid load, impaired renal reserve, urinary tract changes	eGFR decline, nephrolithiasis, renal deterioration	Baseline renal function strongly influences the severity of metabolic complications	Sperling et al. (1); Tinoco et al. (11)
Intestinal complications	Bowel resection, altered bile acid handling, changed transit	Diarrheal, bloating, malabsorption	Gastrointestinal symptoms are influenced by the bowel segment used and diversion type	Chesnut et al. (2); Barone et al. (3)
Nutritional deficiencies	Ileal resection, impaired absorption, chronic diarrhoea	Vitamin B12 deficiency, anaemia, malnutrition	Long-term follow-up should include nutritional assessment, especially after ileal diversion	Sperling et al. (1); Chesnut et al. (2)
Bone metabolism disorders	Chronic acidosis, calcium buffering, vitamin D disturbance	Osteopenia, osteoporosis, fractures	Chronic metabolic acidosis may contribute to skeletal demineralization over time	Sperling et al. (1); Hautmann (5)

Abbreviations: SIBO, small intestinal bacterial overgrowth.

and continent reconstruction. Imaging should be interpreted together with serum creatinine and estimated glomerular filtration rate, because serum creatinine alone may underestimate functional decline in patients with low muscle mass (4, 8, 11).

Stone formation is another clinically relevant complication. Altered urinary pH, chronic bacteriuria, urinary stasis, mucus, foreign material, and metabolic abnormalities may promote calculi. Adequate hydration, correction of acidosis, investigation of recurrent infection, and prompt treatment of obstruction are central preventive measures (1, 11).

Preservation of renal function therefore depends on both surgical and medical follow-up: early recognition of obstruction, infection, stones, dehydration,

and metabolic acidosis; serial biochemical assessment; and risk-adapted upper urinary tract imaging throughout long-term follow-up (1, 4, 8). Table 2 compares the metabolic and intestinal consequences of the principal diversion types.

Intestinal Complications and Small Intestinal Bacterial Overgrowth (SIBO)

Using intestinal segments for urinary reconstruction alters gastrointestinal anatomy and physiology. Most patients adapt, but some develop persistent diarrhoea, bloating, abdominal discomfort, altered bowel habits, or malabsorption. Severity depends on the segment and length of bowel resected or excluded, baseline gastrointestinal function, motility, medication exposure, and postoperative adaptation (1–3).

Table 2. Metabolic and intestinal consequences according to the type of urinary intestinal diversion

Type of urinary diversion	Intestinal segment used	Major metabolic considerations	Potential intestinal consequences	Long-term monitoring priorities
Ileal conduit	Short ileal segment	Hyperchloremic metabolic acidosis may occur but is generally less pronounced than in continent diversions	Mild bowel dysfunction; possible vitamin B12 deficiency after long-term follow-up	Renal function, electrolytes, acid–base status, vitamin B12
Orthotopic neobladder	Longer ileal segment	Increased risk of metabolic acidosis due to prolonged urine–bowel contact	Malabsorption, diarrhoea, vitamin B12 deficiency, possible SIBO	Renal function, serum bicarbonate, nutritional status, vitamin B12
Continent cutaneous reservoir	Ileum with or without colon	Electrolyte disturbances and metabolic acidosis may develop depending on bowel length and renal reserve	Altered bowel function and nutritional deficiencies in selected patients	Electrolytes, renal function, nutritional assessment
Colon-based diversion	Colonic segment	Greater chloride absorption and bicarbonate loss may increase the risk of hyperchloremic metabolic acidosis	Changes in bowel habit, diarrhoea, electrolyte imbalance	Acid–base status, electrolytes, renal function, gastrointestinal symptoms

Abbreviations: SIBO, small intestinal bacterial overgrowth.

Chronic diarrhoea is one of the most common gastrointestinal complaints. Ileal resection or exclusion may impair bile acid reabsorption and accelerate transit, increasing stool frequency and fluid loss. More extensive bowel utilisation may further reduce absorptive reserve and contribute to electrolyte depletion, dehydration, and nutritional imbalance (2, 6).

The preferred non-invasive diagnostic approach is standardised glucose or lactulose hydrogen-methane breath testing. Before testing, generally avoid antibiotics for four weeks, pro-motility agents and laxatives for one week for four weeks, promotility agents and laxatives for one week, fermentable foods for the preceding day, and food for 8–12 hours. Standard substrates are 75 g glucose or 10 g lactulose. A rise in hydrogen of at least 20 parts per million within 90 minutes supports SIBO, while methane of at least 10 parts per million at any time is more accurately termed intestinal methanogen overgrowth. In selected cases, quantitative duodenal aspirate culture of at least 10^3 colony-forming units/mL may sup-

port the diagnosis, but it is invasive and not a universally available gold standard (7).

Treat confirmed symptomatic SIBO rather than observe it without intervention. Management includes correcting the underlying anatomical or motility disorder where feasible, replacing nutritional deficiencies, providing hydration and dietary support, and an individualised course of antibiotics.

Rifaximin is the most studied minimally absorbed agent; systemic alternatives may be used according to clinical context, local antimicrobial policy, contraindications, and suspected microbial pattern. Avoid empirical repeated antibiotic courses without reassessment because recurrence is common and evidence for a single universal regimen is limited. Consider repeat breath testing when symptoms persist or recur (7, 12).

SIBO can contribute to malabsorption of vitamin B12 and fat-soluble vitamins, anaemia, weight loss, and chronic fatigue. Small observational studies

have also linked SIBO to reduced bone mineral density, suggesting that long-standing malabsorption may act as a cofactor in metabolic bone disease rather than an isolated direct cause. Recent evidence also shows a higher prevalence of SIBO in chronic liver disease, although causality and the benefit of routine screening in asymptomatic patients remain uncertain (13, 14).

Nutritional Deficiencies and Anaemia

Nutritional complications after urinary intestinal diversion primarily relate to ileal segment use altered in gastrointestinal physiology, and changes in nutrient absorption. Although many patients remain clinically stable for years after surgery, deficiencies may develop gradually and become apparent only during long-term follow-up. Their recognition is particularly important because several of these abnormalities are preventable or readily treatable when identified early (1, 8).

Vitamin B12 deficiency is the best recognised micronutrient disorder. Absorption occurs in the terminal ileum, and resection or functional exclusion of this segment may impair uptake. Because hepatic stores are substantial, deficiency may become clinically apparent only several years after surgery. Untreated deficiency can cause megaloblastic anaemia, cognitive impairment, peripheral neuropathy, and irreversible neurological injury, supporting regular laboratory assessment in patients with ileal diversion (4, 8, 15).

Iron deficiency and anaemia may also occur, although their ethology is usually multifactorial. Reduced intake, chronic inflammation, recurrent infection, occult blood loss, chronic kidney disease, and impaired intestinal absorption may all contribute. Persistent diarrhoea or SIBO may further compromise uptake of micronutrients required for erythropoiesis (1, 6, 7).

Patients with extensive ileal resection or exclusion may additionally develop impaired bile acid recyc-

ling and fat absorption. These alterations can cause chronic diarrhoea, weight loss, and deficiencies of vitamins A, D, E, and K. Risk increases with the amount of bowel affected and with coexisting motility disorders, SIBO, pancreatic disease, or chronic liver disease (6, 7, 14).

Long-term follow-up should include complete blood count and vitamin B12 measurement, with additional iron studies, folate, albumin, magnesium, and fat-soluble vitamin assessment guided by symptoms, diversion type, bowel length, liver disease, and nutritional risk. Correct deficiencies promptly, and evaluate unexplained abnormalities for malabsorption, SIBO, infection, bleeding, or renal disease (4,6–8,15).

Bone Metabolism, Osteoporosis, and Fracture Risk

Long-term alterations in bone metabolism have been increasingly recognised as clinically relevant complications of urinary intestinal diversion. Chronic metabolic acidosis, impaired renal function, and nutritional deficiencies interact to promote skeletal demineralisation and increase the risk of osteoporosis and fragility fractures. Although these changes often develop gradually, they may substantially affect morbidity in patients with prolonged postoperative survival (1, 11, 16).

A key mechanism underlying bone loss is persistent hyperchloremic metabolic acidosis. To buffer excess hydrogen ions, bone releases alkaline salts, mobilising calcium and phosphate from the skeleton. Sustained acid retention may therefore stimulate bone resorption, reduce bone mineral density, and impair normal mineralisation. In parallel, urinary calcium excretion may increase, further contributing to negative calcium balance and progressive skeletal weakening (1, 5).

Vitamin D deficiency and impaired intestinal absorption may amplify the skeletal effects of chronic acidosis. Patients with ileal resection, chronic diarrhoea, SIBO, or chronic liver disease may have

reduced absorption or altered vitamin D and calcium metabolism. Evidence linking SIBO directly to osteoporosis is limited to small observational studies; therefore, it should be regarded as a potential cofactor through malabsorption and poor nutritional status rather than as an established independent cause (6, 13, 14).

Population-based evidence supports the clinical relevance of skeletal complications. Patients with intestinal urinary diversion have a higher reported incidence of bone loss and fragility fractures than matched controls, consistent with the combined effects of chronic acidosis, renal impairment, age, hypogonadism, and nutritional deficiency (4, 16).

Bone-health surveillance should be risk-adapted. Assess serum calcium, phosphate, alkaline phosphatase, renal function, and 25-hydroxyvitamin D in patients with persistent acidosis, malabsorption, chronic liver or kidney disease, premature menopause, symptomatic hypogonadism, low-trauma fracture, or other osteoporosis risk factors. Dual-energy X-ray absorptiometry is appropriate when standard clinical criteria or these additional risks are present (1, 4, 9, 10, 16).

Chronic Liver Disease and Perioperative Risk

Chronic liver disease is not a consequence of urinary diversion, but it substantially modifies the safety of radical cystectomy and bowel-based reconstruction. Cirrhosis increases vulnerability to bleeding, infection, acute kidney injury, malnutrition, impaired wound healing, hepatic decompensation, and postoperative mortality. Contemporary radical cystectomy data demonstrate higher morbidity and mortality with increasing Model for End-Stage Liver Disease (MELD) score, and recent population-based evidence identifies chronic liver disease as an independent risk factor for adverse in-hospital outcomes (17, 18).

Preoperative assessment should establish whether liver disease is compensated or decompensated and

should include bilirubin, albumin, international normalised ratio, creatinine, sodium, platelet count, nutritional status, and evidence of portal hypertension, ascites, encephalopathy, or prior variceal bleeding. MELD and Child-Pugh classification provide useful baseline information, but current hepatology guidance recommends multidimensional surgery-specific risk assessment rather than reliance on a single score (19).

Elective surgery should be planned jointly by urology, anaesthesia, hepatology, nutrition, and, when needed, nephrology. Modifiable factors such as ascites, infection, alcohol use, malnutrition, electrolyte abnormalities, and renal dysfunction should be optimised. A MELD score of 10 or greater is a clinically relevant warning signal in radical-cystectomy cohorts, but it is not an absolute contraindication; the decision should consider cancer urgency, hepatic reserve, portal hypertension, frailty, and alternative oncologic strategies (17, 19).

Urinary diversion should be individualised. In patients with limited hepatic, renal, or nutritional reserve, a shorter and technically simpler bowel segment may reduce physiological burden, but direct comparative evidence in cirrhosis is insufficient to mandate one diversion for all patients. Postoperative surveillance should include liver function, coagulation, renal function, nutrition, infection, and signs of hepatic decompensation in addition to standard diversion follow-up (18, 19).

CLINICAL MONITORING AND MANAGEMENT STRATEGIES

Long-term success after urinary intestinal diversion depends on structured surveillance rather than surgical technique alone. Because many abnormalities are initially asymptomatic, follow-up should combine scheduled core assessments with more intensive, symptom- and risk-triggered testing. No single universally validated schedule exists; the protocol below synthesises available urological, nephrological, gastroenterological, hepatological, and endocrine guidance (1, 4, 7–10, 12, 19).

Metabolic and Renal Monitoring

Routine laboratory assessment should include serum electrolytes, bicarbonate, creatinine, estimated glomerular filtration rate, and, when bicarbonate is low or symptoms are disproportionate, venous blood gas analysis. Persistent hyperchloremic metabolic acidosis should prompt evaluation of hydration, renal function, infection, and obstruction. Oral alkali therapy may be indicated when acidosis is sustained, with dose and monitoring individualised to renal function and electrolyte status (1,8,11).

Upper urinary tract imaging should be integrated with oncologic surveillance and continued long term to identify hydronephrosis, ureteroenteric stricture, stones, or progressive structural deterioration. New renal dysfunction, recurrent infection, flank pain, or reduced stoma/neobladder drainage warrants expedited imaging and urological assessment (4,8,11).

Nutritional and Gastrointestinal Follow-up

Long-term nutritional surveillance is recommended, particularly after ileal diversion or extensive bowel surgery. Measure Vitamin B12 annually, as recommended by current European urological guidance. Add a complete blood count, iron studies, folate, albumin, magnesium, and fat-soluble vitamins based on symptoms and risk. Persistent diarrhoea, bloating, weight loss, or unexplained deficiency should trigger evaluation for bile acid malabsorption, SIBO, pancreatic disease, infection, and other causes (4, 6–8,1 5).

Dietary counselling and individualised nutritional support should address hydration, stool losses, energy and protein intake, and documented deficiencies. SIBO testing is symptom-triggered rather than routine. Treat confirmed symptomatic SIBO and address the underlying predisposing factor; recurrence should prompt reassessment rather than indefinite empirical antibiotic therapy (7, 12).

Bone Health Assessment

Patients with chronic acidosis or additional osteoporosis risk factors should undergo periodic assessment of calcium, phosphate, alkaline phosphatase, 25-hydroxyvitamin D, renal function, and relevant endocrine status. Dual-energy X-ray absorptiometry should follow standard osteoporosis criteria and be considered earlier in patients with fragility fracture, premature surgical menopause, confirmed hypogonadism, chronic liver or kidney disease, persistent malabsorption, or recurrent acidosis (4, 9, 10, 13, 16).

Chronic Liver Disease Monitoring

Patients with known or suspected chronic liver disease require preoperative and postoperative hepatology input. Monitoring should include bilirubin, albumin, international normalised ratio, aminotransferases, alkaline phosphatase, platelet count, renal function, sodium, nutrition, and clinical evidence of ascites, encephalopathy, infection, or portal-hypertensive complications. Frequency should be determined by disease severity and recent decompensation (17–19).

Sex-Specific Functional and Endocrine Follow-up

Sexual function, continence, voiding or emptying, pelvic-floor symptoms, and quality of life should be assessed in both women and men. Women who undergo bilateral oophorectomy before the expected age of natural menopause should be evaluated for vasomotor symptoms, genitourinary syndrome of menopause, cardiovascular and bone risk, and candidacy for menopausal hormone therapy. Systemic therapy may be appropriate after individualised oncologic and vascular risk assessment, particularly in non-hormone-sensitive malignancy, while low-dose vaginal estrogen is an effective option for isolated genitourinary symptoms. Testosterone therapy in women should not be used routinely for cardiovascular or muscle protection and is reserved for carefully assessed hypoactive sexual desire disorder (9).

In men, testosterone deficiency should be diagnosed only when compatible symptoms or signs coexist with consistently low morning total testosterone on two separate measurements. A value below 300 ng/dL is a reasonable diagnostic support threshold in the AUA guideline. Testosterone replacement is therefore not mandatory after RC or UD; it is an individualised treatment for confirmed symptomatic deficiency after assessment of fertility plans, haematocrit, cardiovascular status, prostate or breast cancer risk, sleep apnea, and other contraindications, with appropriate on-treatment monitoring (10).

Proposed Risk-Adapted Screening Protocol

The following schedule is a pragmatic synthesis rather than a validated universal standard. Modify it

according to diversion type, bowel length, baseline kidney and liver function, age, frailty, oncologic surveillance, and previous complications. Table 3 presents the proposed risk-adapted schedule.

Multidisciplinary Care

Optimal care may require urologists, nephrologists, gastroenterologists, hepatologists, endocrinologists or gynaecologists, dietitians, physiotherapists, and primary care clinicians. A coordinated plan is particularly important for patients with renal or liver disease, persistent gastrointestinal symptoms, malnutrition, recurrent acidosis, osteoporosis, surgical menopause, symptomatic hypogonadism, or complex functional problems.

Table 3. Proposed risk-adapted screening protocol after urinary intestinal diversion

Time point	Core assessment	Additional risk- or symptom-triggered assessment
Preoperative baseline	CBC; sodium, potassium, chloride, bicarbonate; creatinine/eGFR; calcium; albumin; urinalysis as indicated; upper-tract imaging; nutritional and functional history.	Liver panel, INR, platelets, MELD/Child-Pugh and hepatology review if liver disease; vitamin B12 and 25-OH vitamin D in high-risk patients; sex-specific endocrine history.
Approximately 3 months	Electrolytes, bicarbonate, creatinine/eGFR, hydration and stoma/neobladder function; review infection, obstruction, bowel symptoms, weight, and medications.	Venous blood gas if bicarbonate is low; imaging for renal deterioration, pain, infection, or poor drainage; nutritional tests if diarrhoea or weight loss.
6–12 months	Repeat renal and metabolic laboratory profile; upper-tract assessment coordinated with oncologic imaging; CBC and nutritional review.	SIBO breath test for persistent bloating/diarrhoea or unexplained deficiency; liver monitoring according to disease severity; DXA if clinically indicated.
Annually lifelong	Renal function, electrolytes and bicarbonate; annual vitamin B12; review infections, stones, bowel function, hydration, weight, continence/emptying, sexual function, and quality of life.	Iron/folate/fat-soluble vitamins, 25-OH vitamin D, DXA, hormone testing, or more frequent imaging according to risk and prior abnormalities.
At any new symptom or abnormal result	Prompt evaluation rather than waiting for the next scheduled visit.	Assess obstruction, infection, acidosis, dehydration, SIBO/malabsorption, hepatic decompensation, nutritional deficiency, or endocrine dysfunction as clinically appropriate.

Abbreviations: CBC, complete blood count; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; 25-OH vitamin D, 25-hydroxyvitamin D; SIBO, small intestinal bacterial overgrowth.

DISCUSSION

This review confirms that metabolic and intestinal complications remain central to long-term care after urinary intestinal diversion. The physiological consequences of exposing bowel mucosa to urine interact with obstruction, infection, hydration, renal reserve, nutritional status, liver disease, age, and endocrine factors. Many complications are preventable or modifiable when surveillance begins before symptoms become advanced (1, 3, 4, 8).

Hyperchloremic metabolic acidosis is the most consistent unifying mechanism. It should not be regarded as an isolated laboratory finding, because persistent acid retention can aggravate muscle weakness, renal dysfunction, calcium loss, and skeletal demineralisation. The association supports routine measurement of bicarbonate and renal function, with investigation and treatment of sustained abnormalities (1, 5, 8).

Risk is highly individualised. Baseline kidney function, bowel segment and length, urine-bowel contact time, obstruction, infection, age, frailty, chronic liver disease, and nutritional reserve all modify outcomes. A uniform protocol is therefore less appropriate than a core lifelong schedule intensified according to risk and previous complications (1, 4, 8, 11, 17–19).

Gastrointestinal symptoms deserve systematic attention. SIBO is clinically plausible after anatomical and motility changes, but symptoms alone are not diagnostic. Standardised breath testing before treatment improves diagnostic discipline, while management should address the underlying cause and documented deficiencies in addition to antibiotic therapy. Evidence connecting SIBO with osteoporosis or liver disease supports clinical vigilance but does not establish a direct causal pathway in every patient (7, 12–14).

Nutritional deficiencies may remain silent for years. Vitamin B12 depletion is especially important because neurological injury may be irreversible. Annual measurement is a practical minimum after

bowel diversion, while broader testing should be guided by diarrhoea, weight loss, anaemia, bowel length, SIBO, chronic liver disease, and other indicators of malabsorption (4, 8, 15).

Bone health reflects the cumulative effects of acidosis, renal impairment, vitamin D and calcium deficiency, malabsorption, age, inactivity, surgical menopause, and confirmed hypogonadism. Hormone therapy may contribute to bone preservation in appropriately selected patients, but neither menopausal hormone therapy nor testosterone replacement should be presented as mandatory or as a universal preventive strategy after cystectomy (9, 10, 16).

This review has several limitations. The literature is heterogeneous in design, diversion type, baseline risk, and follow-up. Evidence specifically addressing SIBO, chronic liver disease, and endocrine therapy after urinary diversion is limited, and several recommendations are extrapolated from broader gastroenterology, hepatology, and endocrine guidelines. We excluded publications focused primarily on chemotherapy- or radiotherapy-related toxicity when diversion-specific effects could not be separated therefore, the review does not quantify the independent contribution of these oncologic treatments. The proposed screening protocol is a pragmatic synthesis and requires prospective validation.

Overall, the evidence supports a multidisciplinary model in which metabolic monitoring, renal function preservation, upper-tract surveillance, nutritional assessment, symptom-directed SIBO evaluation, bone health, hepatic risk, and sex-specific functional or endocrine care are integral components of long-term management.

CONCLUSION

Urinary intestinal diversion remains indispensable after radical cystectomy and in selected complex pelvic or lower urinary tract conditions. Diversion type, bowel length, renal and hepatic reserve, nutritional status, infection, obstruction, and individual

patient characteristics influence its long-term consequences.

Hyperchloremic metabolic acidosis is a key mechanism linking electrolyte abnormalities, renal impairment, muscle symptoms, and skeletal deterioration. Gastrointestinal disorders, including bile acid diarrhoea, malabsorption, and SIBO, may further compromise nutrition and bone health. Test SIBO objectively in symptomatic patients where feasible, and treat confirmed symptomatic disease alongside underlying causes and deficiencies.

Successful management requires lifelong, risk-adapted assessment of renal function, acid-base balance, upper urinary tract integrity, vitamin B12 and other nutritional markers, gastrointestinal symptoms, and bone health. Patients with chronic liver disease require multidisciplinary perioperative risk assessment, while hormone replacement therapy should be individualised for documented surgical menopause or symptomatic hypogonadism rather than used routinely in all patients.

Prospective studies are needed to validate surveillance intervals and clarify the incidence and clinical impact of SIBO, hepatic comorbidity, and endocrine dysfunction across diversion types. Until such evidence is available, structured multidisciplinary follow-up and early correction of modifiable abnormalities offer the best strategy to reduce morbidity and preserve long-term quality of life.

Use of Generative Artificial Intelligence

During manuscript preparation, OpenAI ChatGPT was used for language editing, translation support, and assistance in organising literature searches and manuscript structure. The human authors reviewed and approved all scientific statements, references, and final wording and take full responsibility for the manuscript's accuracy, integrity, and originality.

Conflict of Interest

Conflict of Interest: none declared.

References

1. Sperling CD, Lee DJ, Aggarwal S. Urinary Diversion: Core Curriculum 2021. *Am J Kidney Dis.* 2021;78(2):293–304.
2. Chesnut GT, Rentea RM, Leslie SW. Urinary Diversions and Neobladders. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2026 Jul 24]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK560483/>
3. Barone B, Napolitano L, Reccia P, Calace FP, De Luca L, Olivetta M, et al. Advances in urinary diversion: from cutaneous ureterostomy to orthotopic neobladder reconstruction - a comprehensive review. *J Pers Med.* 2024;14(4):392.
4. European Association of Urology. EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Arnhem: EAU Guidelines Office; 2026 [cited 2026 Jul 24]. Available from: <https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer>.
5. Hautmann RE, Hautmann SH, Hautmann O. Complications associated with urinary diversion. *Nat Rev Urol.* 2011;8(12):667-677.
6. Camilleri M. Advances in understanding of bile acid diarrhea. *Expert Rev Gastroenterol Hepatol.* 2014;8(1):49-61.
7. Pimentel M, Saad RJ, Long MD, Rao SSC. ACG clinical guideline: small intestinal bacterial overgrowth. *Am J Gastroenterol.* 2020;115(2):165-178.
8. Kaufmann E, Black PC, Catto JWF, Djaladat H, Ghodoussipour S, Hamilton-Reeves JM, et al. Functional follow-up after cystectomy and urinary diversion: a narrative review. *JU Open Plus.* 2023;1(11):e00071.
9. The 2022 Hormone Therapy Position Statement of The North American Menopause Society Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause.* 2022;29(7):767-794.
10. Mulhall JP, Trost LW, Brannigan RE, Kurtz EG, Redmon JB, Chiles KA, et al. Evaluation and management of testosterone deficiency: AUA guideline. *J Urol.* 2018;200(2):423-432.
11. Tinoco CL, Lima E. Urinary diversions for radical cystectomy: a review of complications and their management. *Mini-invasive Surg.* 2021;5:28.
12. Quigley EMM, Murray JA, Pimentel M. AGA Clinical Practice Update on Small Intestinal Bacterial Overgrowth: Expert Review. *Gastroenterology.* 2020;159(4):1526-1532.
13. Stotzer PO, Johansson C, Mellstrom D, Lindstedt G, Kilander AF. Bone mineral density in patients with small intestinal bacterial overgrowth. *Hepatogastroenterology.* 2003;50(53):1415-1418.
14. Shah A, Spannenburg L, Thite P, Morrison M, Fairlie T, Koloski N, et al. Small intestinal bacterial overgrowth in chronic liver disease: an updated systematic review and meta-analysis of case-control studies. *EClinicalMedicine.* 2025;80:103024.
15. Terai A, Okada Y, Shichiri Y, Takechi Y, Terachi T, Arai Y. Vitamin B12 deficiency in patients with urinary intestinal diversion. *Int J Urol.* 1997;4(1):21-25.
16. Pozo C, Pradere B, Rebhan K, Chao C, Yang L, Abufaraj M, et al. Impact of intestinal urinary diversion on the risk of fracture and loss of bone mass: a systematic review. *Bladder Cancer.* 2021;7(3):365-376.
17. Ayoub CH, Dakroub A, El-Asmar JM, Hajj Ali A, Beaini H, Abdulfattah S, et al. Preoperative MELD score predicts mortality and adverse outcomes following radical cystectomy: analysis of the American College of Surgeons National Surgical Quality Improvement Program. *Ther Adv Urol.* 2022;14:17562872221135944.
18. Polverino F, Marmioli A, Longoni M, Le QC, Falkenbach F, Nicolazzini M, et al. The effect of chronic liver disease on adverse in-hospital outcomes after radical cystectomy and ileal conduit urinary diversion. *Ann Surg Oncol.* 2025;32(13):10328-10334.
19. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on extrahepatic abdominal surgery in patients with cirrhosis and advanced chronic liver disease. *J Hepatol.* 2025;83(3):768-789.



Acute liver injury associated with the consumption of a neem-containing food supplement (*Azadirachta indica*): a case report

Akutna jetrna okvara, povezana z uživanjem prehranskega dopolnila z indijsko melijo (*Azadirachta indica*): prikaz primera

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Ključne besede: hepatotoksičnost, nutrивigilanca, z zdravili povzročena jetrna okvara, samozdravljenje.

ABSTRACT

Food supplements are classified as foods intended to supplement the normal diet. They are regulated by general food legislation, which requires all foods placed on the market, including food supplements, to be safe for consumption. As these products are generally not subject to a pre-market assessment of quality, safety and efficacy comparable to that required for medicinal products, it is important to moni-

IZVLEČEK

Prehranska dopolnila sodijo med živila, namenjena dopolnjevanju običajne prehrane. Njihovo področje ureja splošna živilska zakonodaja, ki določa, da morajo biti vsa živila, vključno s prehranskimi dopolnili, ki so dana na trg, varna za uživanje. Ker ti izdelki pred trženjem praviloma niso predmet presoje kakovosti, varnosti in učinkovitosti, primerljive s presojo, ki velja za zdravila,

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tor their safety after they have entered the market. Namely, food supplements may vary in quality and may contain substances in forms and/or quantities that could adversely affect human health. From a safety perspective, particular attention is paid to food supplements containing botanical ingredients, especially (medicinal) plants and preparations derived from them, such as extracts. Because of their natural origin, consumers may perceive these products as a safer alternative to synthetic medicinal products and may also use them for self-treatment. The main composition-related risk factors include the intrinsic toxicity of botanical ingredients, the presence of contaminants, and the presence of undeclared pharmacologically active substances and unauthorised substances. Nutrivigilance is a vigilance scheme for food aimed at improving consumer safety through the rapid identification of possible adverse effects associated with the consumption of specific foods. In Slovenia, the nutrivigilance system primarily monitors adverse effects associated with the consumption of food supplements. In this article, we present a case of acute liver injury associated with the consumption of a food supplement containing neem (*Azadirachta indica*), which the patient used to self-treat psoriasis.

je pomembno, da njihovo varnost spremljamo tudi po prihodu na trg. Lahko so namreč različne kakovosti in vsebujejo snovi v takšnih oblikah in/ali količinah, da lahko škodljivo vplivajo na zdravje ljudi. Z vidika varnosti je posebna pozornost namenjena prehranskim dopolnilom, ki vsebujejo rastlinske sestavine, zlasti (zdravilne) rastline in njihove pripravke, na primer izvlečke. Zaradi naravnega izvora jih uporabniki lahko dojemajo kot varnejšo alternativo sintetičnim zdravilom in jih uporabljajo tudi za samozdravljenje. Med glavne dejavnike tveganja, povezane s sestavo, sodijo intrinzična toksičnost rastlinskih sestavin, prisotnost onesnaževal ter vsebnost nedeklariranih farmakološko aktivnih snovi in neodobrenih snovi. Nutrivigilanca je vigilančna shema za živila, katere namen je izboljšati varnost potrošnikov s hitrim prepoznavanjem možnih neželenih učinkov, povezanih z uživanjem določenih živil. V Sloveniji v okviru sistema nutrivigilance spremljamo predvsem neželene učinke, povezane z uživanjem prehranskih dopolnil. V prispevku predstavljamo primer akutne jetrne okvare, povezane z uživanjem prehranskega dopolnila z indijsko melijo (*Azadirachta indica*), ki ga je bolnica uporabljala za samozdravljenje psoriaze.

INTRODUCTION

Food supplements (FSs) containing botanical ingredients – including plants, algae, fungi, or lichens, and preparations derived from them (1) – represent a rapidly expanding food market sector, characterised by a substantial increase in commercially available products and growing consumer acceptance (2). Owing to their natural origin and perceived safety, these products are frequently used for self-treatment, based on the assumption that they may be as effective as conventional medicines while posing a lower risk of adverse effects (3). This perception may encourage prolonged or long-term use, often without disclosure to health-care professionals. However, botanicals, particularly in extract form, can exert biologically relevant

effects that, depending on dose and quality of the ingredients, may be physiological, therapeutic, or toxic (2).

Several botanical ingredients used in FSs have been implicated in hepatotoxicity, including kava-kava (*Piper methysticum* G. Forst.), green tea extracts (*Camellia sinensis* L.) (4), ashwagandha (*Withania somnifera* (L.) Dunal), *Garcinia cambogia* (Gaertn.) Desr., and oral turmeric-containing formulations (5). This concern is supported by data from the French nutrivigilance system collected by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) between 2009 and 2016, which identified the liver as the most frequently affected organ, accounting for 67% of the 92 reported adverse effects likely to be associated

with the consumption of FSs containing selected plant species (6). The spectrum of liver injury following exposure to these products is broad, ranging from asymptomatic elevations of liver enzymes to acute or chronic hepatitis and, in severe cases, acute liver failure which can be fatal (7). Although causality is often difficult to establish in individual cases, FSs containing botanical ingredients should be considered among the potential contributors in the differential diagnosis of drug-induced liver injury (DILI). Most cases of DILI are idiosyncratic (8), making this condition one of the most challenging disorders encountered in clinical hepatology.

Azadirachta indica A. Juss. (neem) is incorporated into several polyherbal Ayurvedic preparations (9), and neem extracts are also marketed as FSs. Although neem-associated hepatotoxicity appears to be a rare cause of clinically apparent liver injury (10), the increasing consumption of FSs containing botanical ingredients highlights the importance of recognizing and reporting potential adverse hepatic effects.

We report a case of acute hepatitis occurring after the consumption of a neem-containing FS in an adult female admitted to the Department of Gastroenterology and Hepatology, University Medical Centre Ljubljana, for evaluation of unexplained liver injury.

CASE REPORT

A 53-year-old female patient was referred to our department after abnormal liver function tests were detected 4 days before admission at a community health centre: total bilirubin 1.5 mg/dL, aspartate aminotransferase (AST) 1775 U/L, alanine aminotransferase (ALT) 2507 U/L, alkaline phosphatase (ALP) 192 U/L, and gamma-glutamyl transferase (GGT) 172 U/L. On admission, the patient was asymptomatic, afebrile, and denied abdominal pain. Mild evening fatigue and intermittent dizziness were the only reported symptoms. Physical examination was unremarkable.

Over the preceding months, she had intentionally lost 3 kg of body weight. She denied known allergies, excessive alcohol consumption, smoking, and recent travel. Family history was notable for alcohol-associated liver disease in her father. The patient had been diagnosed with psoriasis at the age of 14 years. Detailed history taking revealed that she had been consuming a neem-containing FS at a dose of one teaspoon daily before meals for four months as a self-treatment for psoriasis. The product, purchased as a botanical preparation, was labelled as containing *A. indica* as the sole ingredient. The supplement was discontinued four days before admission due to lack of clinical improvement in psoriasis. Two weeks before admission, the patient developed symptoms consistent with a common cold and self-administered Daleron, an over-the-counter paracetamol-containing medication. During the three days preceding admission, the patient also took vitamin supplements, including a vitamin B-complex preparation and a vitamin preparation reported by patient as "Supradyn".

Initial blood work on admission showed a total bilirubin of 2.3 mg/dL, AST 1245 U/L, ALT 2299 U/L, ALP 195 U/L, GGT 225 U/L, and an international normalized ratio (INR) < 1.0. The pattern of liver injury was classified as hepatocellular based on the R-ratio (ALT/ALP, expressed as multiples of their respective upper limits of normal), with a value ≥ 5 (5). Serologic testing excluded acute infection with hepatitis A, B, C, and E viruses, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus type 1 (HSV-1), and varicella-zoster virus (VZV). Immunoglobulin levels were within normal limits. Autoimmune serology revealed weakly positive ANCA IgG (titer 1:20), considered clinically nonspecific in the absence of compatible systemic manifestations, and weakly positive antimitochondrial M2 antibodies (1+). The remainder of the autoimmune liver disease panel was negative. Iron metabolism studies, ceruloplasmin, serum copper, and thyroid hormone levels were unremarkable.

Abdominal ultrasound performed prior to admission showed no abnormalities of the hepatic parenchyma. A small intraluminal gallbladder lesion was identified without signs of cholecystitis; follow-up imaging was recommended in six months. Given the unexplained liver injury, a liver biopsy was performed on day 4 of hospitalization. Histological examination demonstrated features consistent with subacute hepatitis, including patchy portal and interface inflammatory infiltrates, lobular necroinflammatory activity, and focal centrilobular early collagen deposition. The presence of eosinophils within an otherwise predominantly mononuclear inflammatory infiltrate was suggestive of idiosyncratic DILI.

During hospitalization, liver function gradually improved (total bilirubin 1.7 mg/dL, AST 790 U/L, ALT 1182 U/L, ALP 164 U/L, GGT 203 U/L), and the patient was discharged on day 8 in a hemodynamically stable and asymptomatic condition. Follow-up liver function tests demonstrated normalization of hepatic parameters (total bilirubin 0.64 mg/dL and AST 31.8 U/L, ALT 34.8 U/L, ALP 64.8 U/L, and GGT 16.8 U/L), consistent with complete resolution of idiosyncratic DILI.

Causality was assessed using the validated method for determining causality in reports of adverse effects in nutrивigilance, developed by ANSES and applicable to FSs and other foods within the scope of nutrивigilance (11). This method provides a numerical score combining a chronological sub-score – time to onset, resolution after discontinuation, and recurrence upon re-exposure – and an aetiological sub-score assessing alternative causes, resulting in an overall intrinsic score. Based on a compatible onset time, a suggestive clinical course following discontinuation (progression), an absence of re-exposure and a complete aetiological investigation, the liver injury was deemed as very likely associated with neem consumption, corresponding to an intrinsic score of I4 (scale I0–I4, from excluded to very likely). The timing of the other FSs and medications was not compatible

with the onset of liver injury and was therefore scored as I0 (excluded).

DISCUSSION

To the best of our knowledge, this is the first documented case of acute hepatocellular liver injury in an adult very likely associated with the consumption of a neem-containing FS, with causality supported by liver histopathology and a validated nutrивigilance causality assessment method. Although idiosyncratic DILI is uncommon, it remains an important cause of acute and chronic liver disease worldwide. Diagnosis is challenging because no reliable animal models, *in vitro* systems, or specific biomarkers are currently available to predict or identify the condition before biochemical or histopathological abnormalities become apparent, making DILI primarily a diagnosis of exclusion (5).

A. indica, commonly known as neem, is an evergreen tree belonging to the *Meliaceae* family and has been widely used in Indian traditional systems of medicine for centuries (9). Virtually all parts of the tree have been processed to be used for medicinal purposes, due to their rich content of bioactive phytochemicals with reported antiviral, antimicrobial, anti-inflammatory, antiulcer, anticancer, antipyretic, antifungal, and antihyperglycemic properties (12). Consistent with its traditional use, *A. indica* has been primarily employed in the treatment of skin diseases, inflammatory conditions, rheumatic disorders, and fever (13). An aqueous extract of neem leaves has also been reported to be useful in the treatment of psoriasis vulgaris (14). However, the lack of rigorous controlled trials precludes recommendations for its clinical use.

Despite its long history of traditional use and general perception as a safe natural remedy, *A. indica* is listed by the European Food Safety Authority (EFSA) among botanicals of potential concern due to naturally occurring constituents that may pose

risks to human health when present in foods, including FSs (15). Compounds of concern in neem leaves and seeds include azadirachtin, nimbolide, and azadirone, highlighting that natural origin alone should not be equated with safety.

Most reported cases of neem-associated toxicity involve infants and young children exposed to neem oil through oral or nasal administration as part of traditional practices for the treatment of common cold and cough. Clinical manifestations include vomiting, drowsiness, metabolic acidosis, seizures, and toxic encephalopathy (16-18), with fatal outcomes reported in severe cases (16, 17). Histopathological findings in fatal cases included microvesicular steatosis (16, 17), patchy hepatic necrosis (17), mitochondrial damage, and cerebral edema, findings reminiscent of Reye's syndrome (16). Experimental animal studies exposed to samples of the implicated oil reproduced a similar clinical syndrome (19), supporting a causal relationship between neem oil exposure and toxicity. In adults, neem toxicity has been reported less frequently and has primarily occurred in the context of intentional self-harm (20, 21) or accidental exposure in elderly individuals (22), with neurological manifestations being most prominent.

In contrast, orally consumed neem leaf and bark preparations have generally been considered to have low toxicity (13). However, Brett et al. (23) described a 51-year-old male who developed distal renal tubular acidosis following prolonged consumption of large quantities of neem extract for self-treatment of diabetes. During hospitalization, abnormal liver function tests with a predominantly cholestatic pattern were also observed. However, no liver biopsy was performed, limiting definitive assessment of hepatic injury, although this finding suggests potential hepatic effects of orally administered neem preparations in adults.

Unlike previously reported adult cases, we performed a comprehensive diagnostic evaluation for DILI, including liver histopathology and a structural

causality assessment. This provides supportive evidence that prolonged consumption of a neem-containing FS, even when used according to product instructions, may pose a potential risk of hepatotoxicity, particularly given its unclear long-term effects (9). Experimental studies suggest that neem constituents may impair mitochondrial function through uncoupling of oxidative phosphorylation, resulting in reduced ATP production in rat liver mitochondria (24). This mechanism may be relevant to its hepatotoxic potential, although the precise pathophysiological pathway in humans remains unclear. In addition, several risk factors contributing to hepatotoxicity of herbal remedies should be considered. These include botanical misidentification, notably substitution with the more toxic *Melia azedarach* (13), use of an inappropriate plant part, inadequate storage conditions that may alter the native product, adulteration during processing, and mislabelling of the final product (4). Although the consumed product was labelled as a single-ingredient neem preparation, contamination or adulteration cannot be excluded in the absence of chemical analysis. This is particularly relevant for some traditional or Ayurvedic products, where metals and other elements may be present either intentionally or as contaminants (25).

Limitations

Several limitations in this case report should be acknowledged. First, this report describes a single patient, precluding generalisation of the findings. Second, the consumed FS was not chemically analysed; therefore, its composition remains unverified, and the possibility that the observed liver injury was associated with other potentially hepatotoxic constituents, contaminants, adulterants, or misidentified botanical material, rather than neem itself, cannot be excluded.

CONCLUSION

This case report highlights the importance of obtaining a detailed history of FSs and comple-

mentary medicine use in patients presenting with unexplained liver injury. It also suggests that FSs containing *A. indica* may represent a rare and previously underrecognized cause of idiosyncratic DILI in adults. As consumption of FSs containing botanical ingredients is expected to continue increasing worldwide, clinicians should remain vigilant and systematically report suspected clinical cases to national nutrивigilance systems to facilitate early signal detection, and improve consumer safety.

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (no. 0120-312/2026-2711-8).

References

1. EFSA Scientific Committee. Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements, on request of EFSA. EFSA J 2009; 7(9):1249.
2. Colombo F, Restani P, Biella S, et al. Botanicals in functional foods and food supplements: tradition, efficacy and regulatory aspects. Appl Sci 2020; 10:2387.
3. Lopes L, Coimbra MA, Costa MC, et al. Food supplement vitamins, minerals, amino-acids, fatty acids, phenolic and alkaloid-based substances: an overview of their interaction with drugs. Crit Rev Food Sci Nutr 2023; 63(19):4106-40.
4. European Association for the Study of the Liver. EASL clinical practice guidelines: drug-induced liver injury. J Hepatol 2019; 70(6):1222-61.
5. Fontana RJ, Bjornsson ES, Reddy KR, et al. The evolving profile of idiosyncratic drug-induced liver injury. Clin Gastroenterol Hepatol 2023; 21(8):2088-99.
6. Colombo F, Di Lorenzo C, Biella S, et al. Adverse effects to food supplements containing botanical ingredients. J Funct Foods 2020; 72:103990.
7. ANSES. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on a case of fatal fulminant hepatitis associated with consumption of the food supplement Slim Metabol®. <https://www.anses.fr/system/files/NUT2019SA0136EN.pdf> (accessed 26 Jun 2026).
8. Kozielewicz DM, Stalke P, Skrzypek J. Drug-induced liver injury. Part I: classification, diagnosis and treatment. Clin Exp Hepatol 2025; 11(1):25-33.
9. Gopinath H, Karthikeyan K. Neem in dermatology: shedding light on the traditional panacea. Indian J Dermatol 2021; 66(6):706.
10. LiverTox®: Clinical and Research Information on Drug-Induced Liver Injury. Margosa Oil. <https://www.ncbi.nlm.nih.gov/books/NBK547852/> (accessed 10 Jun 2026).
11. ANSES. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on "Updating the method for determining causality in reports of adverse effects in nutrивigilance". <https://www.anses.fr/en/system/files/NUT2018SA0026EN.pdf> (accessed 10 Jun 2026).
12. Page C, Hawes EM. Haemolytic anaemia after ingestion of neem (*Azadirachta indica*) tea. BMJ Case Rep 2013; 2013:bcr2013200890.
13. Van der Nat JM, van der Sluis WG, de Silva KTD, et al. Ethnopharmacognostical survey of *Azadirachta indica* A. Juss (Meliaceae). J Ethnopharmacol 1991; 35(1):1-24.
14. Pandey SS, Jha AK, Kaur V. Aqueous extract of neem leaves in treatment of psoriasis vulgaris. Indian J Dermatol Venereol Leprol 1994; 60(2):63-7.
15. EFSA. The Compendium of Botanicals. <https://data.europa.eu/data/datasets/efsa-botanical-compendium?locale=en> (accessed 10 Jun 2026).
16. Sinniah D, Baskaran G. Margosa oil poisoning as a cause of Reye's syndrome. Lancet 1981; 1(8218):487-9.
17. Sundaravalli N, Bhaskar Raju B, Krishnamoorthy KA. Neem oil poisoning. Indian J Pediatr 1982; 49:357-9.
18. Lai SM, Lim KW, Cheng HK. Margosa oil poisoning as a cause of toxic encephalopathy. Singapore Med J 1990; 31(5):463-5.
19. Sinniah R, Sinniah D, Chia LS, et al. Animal model of margosa oil ingestion with Reye-like syndrome: pathogenesis of microvesicular fatty liver. J Pathol 1989; 159(3):255-64.
20. Suresha AR, Rajesh P, Anil Raj KS, et al. A rare case of toxic optic neuropathy secondary to consumption of neem oil. Indian J Ophthalmol 2014; 62(3):337-9.
21. Iyyadurai R, Surekha V, Sathyendra S, et al. Azadirachtin poisoning: a case report. Clin Toxicol (Phila) 2010; 48(8):857-8.
22. Mishra A, Dave N. Neem oil poisoning: case report of an adult with toxic encephalopathy. Indian J Crit Care Med 2013; 17(5):321-2.
23. Brett J, Beresford R, Sevastos J, et al. Neem extract poisoning as a cause of renal tubular acidosis. J Clin Toxicol 2011; 1:112.
24. Koga Y, Yoshida I, Kimura A, et al. Inhibition of mitochondrial functions by margosa oil: possible implications in the pathogenesis of Reye's syndrome. Pediatr Res 1987; 22(2):184-7.
25. Mikulski MA, Wichman MD, Simmons DL, et al. Toxic metals in ayurvedic preparations from a public health lead poisoning cluster investigation. Int J Occup Environ Health 2017; 23(3):187-92.



Sindrom utesnitve sprednjih kožnih živcev (ACNES)

Anterior Cutaneous Nerve Entrapment Syndrome (ACNES)

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Ključne besede: bolečina trebušne stene, ACNES, kronična bolečina, alodinija

Keywords: abdominal wall pain, ACNES, chronic pain, allodynia

IZVLEČEK

ACNES (ang. Anterior cutaneous nerve entrapment syndrome) je pogosto spregledan vzrok kronične bolečine trebušne stene, ki nastane zaradi utesnitve oziroma draženja sprednjih kožnih vej spodnjih torakalnih živcev. Zanj so značilni lokalizirana bolečina, somatosenzorične spremembe v bolečem predelu ter značilnosti, ki kažejo na izvor bolečine v trebušni steni. Zaradi sočasnih prebavnih simptomov je razlikovanje od visceralne bolečine lahko zahtevno in vodi v obsežno diagnostično obravnavo.

Predstavljamo klinični primer bolnice z dolgotrajno bolečino v epigastriju, napenjanjem in slabostjo ter izrazito preobčutljivostjo kože trebuha. Zaradi klinične slike je bila opravljena obsežna gastroenterološka diagnostika, usmerjena v opredelitev možnih organskih in funkcionalnih vzrokov težav. Ob vztrajanju lokalizirane bolečine in izraziti bolečini že ob

ABSTRACT

ACNES (Anterior Cutaneous Nerve Entrapment Syndrome) is a less commonly recognised cause of chronic abdominal wall pain, caused by the compression or irritation of the anterior cutaneous branches of the lower thoracic nerves. It's characterised by localised pain, sensory changes in the affected area, and features that suggest the pain originates in the abdominal wall.

Because it can present with digestive symptoms, distinguishing it from visceral pain can be tricky and often leads to extensive diagnostic testing.

We present a clinical case of a patient with long-lasting pain in the epigastric area, bloating, and nausea, along with pronounced skin hypersensitivity on the abdomen. Given the clinical picture, we performed extensive gastroenterological diagnostics to identify possible organic and functional causes.

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blagem stiku oblačil s kožo je bil pozneje postavljen sum na ACNES. Primer poudarja pomen celostnega diagnostičnega pristopa k bolniku z bolečino v trebuhu, pri katerem je ob izključevanju drugih možnih vzrokov pomembno prepoznati tudi klinične značilnosti, ki lahko usmerijo sum na ACNES.

With persistent localised pain and significant pain even from light contact of clothing with the skin, ACNES was later suspected. This case highlights the importance of a comprehensive diagnostic approach for a patient with abdominal pain, after ruling out other possible causes, it is important to recognise clinical features that may point to ACNES.

UVOD

Sindrom utesnitve sprednjih kožnih živcev (ACNES) je kronični bolečinski sindrom trebušne stene, ki nastane zaradi utesnitve sprednjih kožnih vej torakalnih živcev ob njihovem prehodu skozi trebušno steno. Čeprav je bolečina pri ACNES somatskega izvora, jo lahko spremljajo tudi gastrointestinalni simptomi, kar otežuje razlikovanje od visceralne bolečine. Klinično prepoznavanje zato temelji na natančni opredelitvi mesta in značilnosti bolečine, oceni senibilitete kože ter usmerjenem pregledu trebušne stene ob sočasnem izključevanju drugih možnih vzrokov težav. Predstavljeni primer ponazarja diagnostični izziv pri bolnici s sočasnimi prebavnimi simptomi in značilnostmi bolečine trebušne stene ter pomen vključitve ACNES v diferencialno diagnostiko dolgotrajne bolečine v trebuhu.

PRIKAZ PRIMERA

36-letna, predhodno zdrava gospa je prvič obravnavana v urgentni zdravstveni ustanovi zaradi nekaj dni trajajoče bolečine v trebuhu, ki jo je zaradi izrazite intenzivnosti ponoči prebudila iz spanja. Lokalizirana je bila v področju žličke in se je širila proti popku. Bolečina je bila krčevita, izrazitejša ob pritisku ter se spreminjala s položajem telesa. Za lajšanje težav je zaužila zaviralec protonske črpalke, analgetik trospij in paracetamol ter antiemetik. Terapija ni olajšala bolečine, težave so vztrajale. Ob tem ji je bilo slabo, bruhalo ni. Povišane telesne temperature, mrzlice, glavobola, bolečine v prsnem košu ni imela. Urin in blato je primerno odvajala. Pred enim letom je bila pregledana pri ginekologu, odstopanj niso ugotavljali.

Gospa dodatno pove da ne more nositi hlač s pasom nad popkom, saj ji postane slabo.

V kliničnem statusu so opisovali bolečinsko prizadetost, abdomen je bil nad nivojem prsnega koša, palpatorno mehak, boleč v epigastriju že ob avskultaciji, še bolj pri palpaciji, peristaltika je bila slišna, ledveni poklep obojestransko neboleč. Odvzeli so kri za laboratorijske preiskave, opravili so še rentgen prsnega koša in abdomna. Pomembnih patoloških odstopanj v laboratorijskih izvidih in izvidih slikovne diagnostike ni bilo. Z namenom opredelitve vzroka bolečine je bil opravljen še ultrazvok trebuha, kljub izraziti klinični sliki preiskava ni razkrila vzroka za bolečine. Gospa je prejela za domov zaviralec protonske črpalke in navodila za gastroezofagelano refluksno bolezen. Po simptomatskem zdravljenju se je bolečina nekoliko umirila, vendar njen vzrok ni bil pojasnjen, zato je bila napotena v nadaljnjo gastroenterološko obravnavo.

Zaradi vztrajajočih težav so opravili predčasno ezofago-gastro-duodenoskopijo, pri kateri so opisali blago eritematozno sluznico želodca, hitri ureazni test je bil negativen. Opisali so veliko ptozo ter oslabljeno peristaltiko želodca. Sumili so na gastroparezo s posledično funkcionalno bolečino. Uvedeno je bilo zdravljenje z zaviralcem protonske črpalke in metoklopramidom ter svetovali so manjše, pogostejše in lahko prebavljive obroke.

Deset dni pozneje je bila gospa zaradi ponovnega poslabšanja ponovno obravnavana v urgentni ambulanti. Bolečina ni bila več stalna, tamveč se je pojavlja v napadih, ki so trajali od nekaj minut do približno treh ur in jih je spremljala slabost.

Ponovno je izpostavljala značilno preobčutljivost trebušne stene, že pritisk hlač ali stik oblačil s trebuhom je sprožil bolečino in slabost.

Ob nadaljnji gastroenterološki obravnavi so ugotovili izrazit meteorizem ter bolečnost v duodenalni točki. Zaradi vztrajanja težav je bila ponovljena gastroskopija z biopsijami in opravljena CT preiskava trebuha, ki je pokazala izrazit meteorizem brez druge patologije. Histopatološki pregled je pokazal blag kronični pangastritis ter blage kronične vnetne spremembe dvanajstnika z limfocitnim duodenitisom, pri čemer število intraepiteljskih celic ni presegalo 30 IEL/ 100 epitelnih celic.

Za nadaljnjo opredelitev težav so opravili dodatne preiskave, med drugimi kapsulno endoskopijo, PCR preiskavo blata na *Giardia lamblia* antigen, genotipizacijo za celiakijo, določitev fekalne elastaze in kalprotektin p ter kontrastno rentgensko preiskavo prebavil. Opravljene preiskave niso pokazale pomembnih odstopanj, pri rentgenu s kontrastom je bila peristaltika želodca primerna, v požiralniku pa blago oslabljena.

Zaradi izrazitega napenjanja in meteorizma, so opravili še dihalni test za SIBO z merjenjem vodika in metana, ki je bil po razpoložljivi dokumentaciji interpretiran kot pozitiven. Uvedli so zdravljenje z rifaksimonom v odmerku 550 mg 2x dnevno za 14 dni, kar na simptomatiko ni imelo vpliva.

Ker etiologijo bolečine še vedno niso dokončno pojasnili, so diagnostično obravnavo dopolnili z endoskopskim ultrazvokom, ki ni pokazal odstopanj ter kolonoskopijo, pri kateri so ugotovili notranje hemoroide in zavrt potek vijug sigme. Uvedeno je bilo zdravljenje s pregabalinom v odmerku 25 mg.

V nadaljevanju so gospo obravnavali tudi pri alergologu. Kožno vbodno testiranje je pokazalo senzibilizacijo za pršico, testi z nutritivnimi alergeni pa so bili negativni, alergijsko etiologijo so ovrgli. Bolnica je ob pregledu opisovala stalno, ostro bolečino v zgornjem delu trebuha med popkom in ksi-

foidom, ki se je občasno izrazito poslabšala. Pri alergologu je prvič omenila, da bolečine ni izzval le pritisk, temveč že blag dotik po koži trebuha.

Zaradi značilnosti bolečine in izrazite preobčutljivosti kože trebuha so prvič posumili na ACNES. Svetovana sta bila pregled v protibolečinski ambulanti z možnostjo diagnostično terapevtske blokade z lokalnim anestetikom ter kontrolna slikovna preiskava (UZ ali MR) z usmerjeno oceno trebušne stene. Carnettov znak in skin-pinch test v razpoložljivi dokumentaciji niso zabeležili.

Izvida obravnave v protibolečinski ambulanti v razpoložljivi dokumentaciji ni bilo, prav tako diagnostično terapevtske infiltracije z lokalnim anestetikom niso izvedli. V nadaljnjem poteku so bolečine postale manj izrazite. Bolnica je prejela pregabalin v odmerku 25 mg zjutraj in 50 mg zvečer, ob dodatku prehranskega pripravka Ensure Plus Advance pa je pridobila štiri kilograme telesne mase. Ob izboljšanju težav je bilo predvideno postopno zmanjšanje odmerka pregabalina.

Leto dni po uvedbi je zdravljenje s pregabalinom postopoma povsem opustila. Sledilo je približno 14 dnevno obdobje izrazitejših težav, nato pa so se simptomi ponovno umirili in ostali primerljivi s stanjem med zdravljenjem. Kljub splošnem izboljšanju je vztrajala lokalna preobčutljivost kože v medialnem delu trebuha, zlasti ob stiku z zadrgo oblačil.

Nadaljnjih rednih kontrol niso predvideli, svetovali so kontrolo po potrebi. Po dostopni dokumentaciji zaradi podobnih bolečin pozneje ni bila ponovno obravnavana.

Diagnostična pot se je zaključila z diagnozo: Druge in neopredeljene bolečine v trebuhu, ACNES?

RAZPRAVA

Predstavljeni primer ponazarja diagnostični izziv pri razločevanju bolečine trebušne stene od bolečine visceralnega izvora, zlasti ob sočasni prisotno-

sti prebavnih simptomov. Pri bolnici so bolečino v epigastriu spremljali izrazito napenjanje, hujšanje ter slabost, kar je utemeljevalo obsežno gastroenterološko obravnavo. Ob vztrajanju lokalizirane bolečine in izrazite preobčutljivosti kože, se je v nadaljnjem poteku diferencialnodiagnostično odprla tudi možnost ACNES.

Patofiziološko ACNES nastane zaradi utesnitve oziroma draženja sprednjih kožnih vej spodnjih torakalnih živcev ob njihovem prehodu skozi trebušno steno, najpogosteje ob lateralnem robu mišice rectus abdominis. Kompresija živca lahko provzroči mehansko ali ishemično draženje in posledično lokalizirano nevropatsko bolečino. (1)

V literaturi so predlagana naslednja diagnostična merila za ACNES: (1)

- enostranska lokalizirana bolečina trebušne stene, ki traja vsaj en mesec;
- prisotnost jasno omejene točke največje občutljivosti, manjše od 2 cm² in lokalizirane znotraj lateralnih meja mišice rectus abdominis;
- somatosenzorične motnje kože v področju boleče točke (hipoestezija, hiperestezija, spremenjeno zaznavanje hladnega dražljaja);
- pozitiven skin-pinch test (izrazita bolečina ob stisku kože nad bolečim mestom);
- pozitiven Carnettov znak (poslabšanje bolečine ob napenjanju trebušnih mišic);
- normalni laboratorijski izvidi, brez znakov vnetja ali okužbe ter brez ugotovljenega kirurškega vzroka bolečine;
- negativne slikovne preiskave trebušne stene;
- začasno zmanjšanje bolečine za vsaj 50 % po aplikaciji lokalnega anestetika v sprožilno točko.

Klinična slika pri predstavljeni bolnici je bila v več elementih skladna z navedenimi diagnostičnimi merili: prisotna je bila dolgotrajna lokalizirana bolečina, spremljana z izrazito preobčutljivostjo kože, opravljene laboratorijske in slikovne preiskave pa niso pokazale vzroka, ki bi v celoti pojasnil klinično sliko. Carnettov test in skin pinch test nista bila dokumentirana, prav tako niso izvedli

predlagano diagnostično terapevtsko infiltracijo z lokalnim anestetikom.

Sočasni prebavni simptomi lahko diagnostično presojo usmerijo predvsem k visceralnemu izvoru bolečine, vendar pri bolnikih z ACES niso redki. Približno polovica bolnikov poroča o visceralnih simptomih, med katerimi so pogosti napihnjenost, slabost, spremembe odvajanja blata in zmanjšan apetit. (2) Njihova prisotnost lahko oteži razlikovanje med bolečino trebušne stene in visceralno bolečino ter prispeva k daljšem diagnostičnem procesu. V raziskavi, ki je zajela 1116 bolnikov z ACNES, je mediana diagnostičnega zamika znašala 18 mesecev. (3)

Možno nevrofiziološko razlago sočasnega pojavljanja somatskih in visceralnih simptomov predstavlja konvergenca somatskih in visceralnih aferentnih poti. Eksperimentalne raziskave kažejo, da lahko somatska in visceralna C-vlakna konvergirajo na iste nevrone v hrbtenjači, kar omogoča medsebojno vplivanje somatskega in visceralnega nociceptivnega procesiranja. Neposredni pomen tega mehanizma za pojav visceralnih simptomov pri ACNES sicer še ni dokončno pojasnjen. (4)

Zdravljenje ACNES poteka stopenjsko in vključuje farkamkološke, intervencijske ter pri vztrajajočih težavah tudi kirurške pristope. Sistemska farmakoterapija se pogosto uporablja kot začetni način obvladovanja kronične oziroma nevropatske bolečine, vendar je njena učinkovitost pri ACNES lahko omejena, saj je osnovni mehanizem težav praviloma mehanska utesnitev oziroma draženje živca. V literaturi so opisani analgetiki, nestoridna protivnetna zdravila, šibki opiodi ter zdravila za zdravljenje nevropatske bolečine, predvsem pregabalin, gabapentin in amitriptilin. (1)

Pri predstavljeni bolnici je bilo uvedeno zdravljenje s pregabalinom, ob katerem so težave sčasoma postale manj izrazite. Po ukinitvi je sledilo prehodno 14 dnevno poslabšanje, nato pa so se težave ponovno umirile in ostale primerljive s stanjem

med zdravljenjem. Kljub splošnemu izboljšanju je vztrajala lokalna preobčutljivost kože ob stiku z oblačili. Zaradi nihanja težav in odsotnosti kontroliranega terapevtskega preizkusa vzročne povezave med izboljšanjem in pregabalinom ni mogoče zanesljivo potrditi.

Pomembno mesto v diagnostično terapevtskem pristopu imajo infiltracije boleče oziroma sprožine točke z lokalnim anestetikom. Postopek ima dvojno vlogo, zmanjšanje bolečine po infiltraciji lahko dodatno podpre diagnozo ACNES, hkrati pa postopek predstavlja terapevtski ukrep. (5) V raziskavah so bile uporabljene infiltracije z 1 % lidokainom, izvedene na slepo ali pod ultrazvočnim nadzorom. Opisane so tudi ponavljajoče se infiltracije v večtedenskih intervalih, pri čemer ob zadovoljivem zmanjšanju bolečine nadaljnje aplikacije lahko opustimo. (6)

Ob nezadostnem ali kratkoročnem učinku infiltracij je ena od nadaljnjih možnosti pulzna radiofrekvenčna terapija (PRF).

V dolgoročnem spremljanju bolnikov, predhodno vključenih v randomizirano raziskavo PULSE, je mediana spremljanja znašala 71,5 meseca. Po eni sami aplikaciji PRF je bil ob koncu spremljanja brez bolečine en bolnik (4,3 %), po ponavljajočih se zdravljenjih s PRF pa še pet bolnikov (21,7 %). V skupini, zdravljeni z nevrektomijo, je bilo brez dodatnega zdravljenja dolgoročno brez bolečine 61,9 % bolnikov. Rezultati kažejo na omejeno dolgoročno učinkovitost PRF pri delu bolnikov, vendar lahko PRF zaradi manjše invazivnosti predstavlja smiselno stopnjo zdravljenja pred kirurškim posegom (7).

Pri vztrajajoči bolečini kljub manj invazivnim postopkom lahko razmislimo o kirurškem zdravljenju, predvsem anteriorni nevrektomiji, pri neuspehu slednje pa je opisana tudi posteriorna nevrektomija. (7)

Pri predstavljeni bolnici so predlagali diagnostično terapevtsko infiltracijo z lokalnim anestetikom, vendar je niso izvedli. Ker so se težave v nadalj-

njem poteku zmanjšale, stopnjevanje zdravljenja z invazivnejšimi metodami ni bilo indicirano.

Predstavljeni primer poudarja pomen celostnega diagnostičnega pristopa k dolgotrajni bolečini v trebuhu, saj prepoznavanje ACNES ob značilni klinični sliki temelji tudi na izključitvi drugih možnih, zlasti visceralnih virov bolečine.

ZAKLJUČEK

ACNES je pomemben diferencialnodagnostični vzrok kronične bolečine v trebuhu. Pri bolniku z dolgotrajno lokalizirano bolečino je treba najprej ustrezno izključiti morebitne visceralne vzroke, zlasti kadar so prisotni tudi gastrointestinalni simptomi. Ob odsotnosti drugega vzroka ter prisotnosti značilnih kliničnih znakov, kot so dobro omejena bolečina in senzorične spremembe kože, je treba pomisliti tudi na ACNES. Prepoznavanje ACNES tako predstavlja pomemben del celostne obravnave bolnika s kronično bolečino v trebuhu.

Literatura

1. Chrona E, Kostopanagiotou G, Damigos D, Batistaki C. Anterior cutaneous nerve entrapment syndrome: management challenges. *J Pain Res.* 2017;10:145–156. doi:10.2147/JPR.S99337.
2. Jacobs MLYE, Janssen L, Stassen LPS, Scheltinga MRM, Roumen RMH. Visceral symptoms in patients with anterior cutaneous nerve entrapment syndrome (ACNES): expression of viscerosomatic reflexes? *Hernia.* 2024;28(1):127–134. doi:10.1007/s10029-023-02827-7.
3. Mol FMU, Maatman RC, De Joode LEGH, Van Eerten P, Scheltinga MR, Roumen R. Characteristics of 1116 consecutive patients diagnosed with anterior cutaneous nerve entrapment syndrome (ACNES). *Ann Surg.* 2021;273(2):373–378. doi:10.1097/SLA.0000000000003224.
4. Luz LL, Fernandes EC, Sivado M, Kokai E, Szucs P, Safronov BV. Monosynaptic convergence of somatic and visceral C-fiber afferents on projection and local circuit neurons in lamina I: a substrate for referred pain. *Pain.* 2015;156(10):2042–2051. doi:10.1097/j.pain.0000000000000267.
5. Boelens OBA, Scheltinga MR, Houterman S, Roumen RM. Randomized clinical trial of trigger point infiltration with lidocaine to diagnose anterior cutaneous nerve entrapment syndrome. *Br J Surg.* 2013;100(2):217–221. doi:10.1002/bjs.8958.
6. Jacobs MLYE, Janssen L, Stassen LPS, Scheltinga MRM, Roumen RMH. Visceral symptoms in patients with anterior cutaneous nerve entrapment syndrome (ACNES): expression of viscerosomatic reflexes? *Hernia.* 2024;28(1):127–134. doi:10.1007/s10029-023-02827-7.
7. ten Have T, van Geffen ST, Zwaans WAR, Maatman RC, Boelens OBA, Steegers MAH, Scheltinga MRM, Roumen RMH. Pulsed radiofrequency or surgery for anterior cutaneous nerve entrapment syndrome: long-term results of a randomized controlled trial. *Pain Pract.* 2024;24(2):288–295. doi:10.1111/papr.13305.



Biomarkerji za ugotavljanje uživanja alkohola in njihova klinična uporabnost

Biomarkers for alcohol consumption and their clinical utility

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Keywords: alcohol, biomarkers, phosphatidylethanol, ethyl glucuronide

IZVLEČEK

Prekomerno uživanje alkohola predstavlja pomemben javnozdravstveni izziv, njegovo prepoznavanje je pogosto oteženo zaradi nezanesljivih ali nepopolnih podatkov v anamnezi. Neposredna biomarkerja fosfatidiletanol (PEth) in etilglukuronid (EtG) omogočata zanesljivejšo oceno uživanja alkohola in dopolnjujeta tradicionalne metode njegovega ugotavljanja. V preglednem članku obravnavamo njune biološke značilnosti, načine določanja, časovna okna zaznavnosti, diagnostično vrednost in dejavnike, ki vplivajo na interpretacijo rezultatov. PEth se določa v krvi in omogoča oceno uživanja alkohola v predhodnih nekaj tednih, medtem ko EtG v urinu zaznava predvsem nedavno uživanje, običajno v zadnjih 24–72 urah. Določanje EtG v lasih in nohtih omogoča retrospektivno oceno uživanja v daljšem, večmesečnem obdobju. Oba biomarkerja sta uporabna pri prepoznavanju škodljivega uživanja alkohola, pri spremljanju abstinence in uspešnosti

ABSTRACT

Excessive alcohol consumption is a major public health problem, and its recognition is often hindered by unreliable information from medical history. The direct biomarkers phosphatidylethanol (PEth) and ethyl glucuronide (EtG) allow a more objective assessment of alcohol consumption and therefore complement traditional methods of detection. In this review, we present their biological characteristics, methods of determination, detection windows, diagnostic value, and the factors that may influence the interpretation of results. PEth is measured in blood and reflects alcohol consumption over the preceding weeks, whereas urinary EtG mainly detects recent drinking, usually within the last 24–72 hours. Determination of EtG in hair and nails allows a retrospective assessment of consumption over a longer period of several months. Both biomarkers are useful for identifying risky and harmful alcohol use and for monitoring abstinence and treatment

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zdravljenja. Njena uporaba je posebej koristna, kadar anamneza ne odraža zanesljivo dejanskega vzorca uživanja alkohola. Kljub veliki diagnostični natančnosti je treba izmerjene vrednosti presojati ob upoštevanju časovnega okna zaznavnosti, mejnih koncentracij, postopka odvzema vzorca in drugih dejavnikov, ki lahko vplivajo na meritve. Biomarkerji ne omogočajo vedno natančne ocene količine zaužitega alkohola in ne nadomeščajo anamneze ali celostne klinične ocene, temveč ju dopolnjujejo. Njihova premišljena uporaba lahko prispeva k zgodnejšemu prepoznavanju škodljivega uživanja alkohola in ustrežnejši obravnavi bolnikov.

outcomes. Their use is particularly valuable when the medical history does not reliably reflect the actual pattern of consumption. Despite their high diagnostic value, results must be interpreted with regard to the detection window, cut-off values, sampling method, and other factors that may affect the measurements. Biomarkers do not always allow an accurate estimate of the amount of alcohol consumed and do not replace the medical history or comprehensive clinical assessment, but complement them. Their considered use can contribute to earlier recognition of harmful alcohol use and more appropriate patient management.

UVOD

Prekomerno uživanje alkohola predstavlja pomemben dejavnik tveganja za razvoj srčnožilnih, jetrnih, malignih in nevroloških bolezni. Zaradi pomembnega vpliva na višjo obolevnost, višjo stopnjo invalidnosti in umrljivosti je prekomerno uživanje alkohola eden glavnih javnozdravstvenih izzivov. Za ustrezno obravnavo bolnika je zato ključnega pomena, da čim bolje ocenimo njihove vzorce uživanja alkohola. Objektivna ocena uživanja alkohola je pomembna ne le pri klinični obravnavi bolnikov, temveč tudi v sodnomedicinskih postopkih, kjer ima lahko prekomerno uživanje alkohola pravne posledice [1].

V klinični praksi zdravnik večinoma presoja stopnjo uživanja alkohola pri bolniku na podlagi dejstev, pridobljenih z anamnezo ali heteroanamnezo. Zanesljivost tako pridobljenih podatkov je omejena, saj so bolniki pri poročanju o količini zaužitega alkohola in pogostosti uživanja alkohola nemalokrat neiskreni. To ima neposreden vpliv na načrtovanje bolnikove obravnave in s tem na bolnikovo prognozo [2, 3, 4]. Zato se v klinični praksi danes vse pogosteje uporabljajo biomarkerji, ki omogočajo objektivnejšo oceno uživanja alkohola. Biomarkerji so fiziološki kazalci izpostavljenosti alkoholu in so tako ključnega pomena za objekti-

vno odkrivanje in spremljanje prekomernega uživanja alkohola [5, 6].

Namen tega preglednega članka je predstaviti fosfatidiletanol in etilglukuronid kot neposredna biomarkerja uživanja alkohola in poudariti njune biološke značilnosti, časovno okno zaznavnosti, občutljivost in specifičnost ter dejavnikov, ki vplivajo na interpretacijo rezultatov. Poleg tega pa je namen izpostaviti njuno uporabnost v klinični praksi pri objektivni prepoznavi in zgodnjem odkrivanju škodljivega uživanja alkohola.

BIOMARKERJI ZA DOKAZOVANJE UŽIVANJA ALKOHOLA

Večina zaužitega alkohola (90–98 %) se s pomočjo alkoholne dehidrogenaze v jetrih presnovi v acetaldehid, ki je toksični metabolit alkohola, ta pa s pomočjo aldehid dehidrogenaze pretvori v acetat. 2–8 % se ga izloči nespremenjenega v izdihanem zraku in urinu. Približno 1,5 % alkohola pa se presnavlja po neoksidativni presnovni poti, kjer nastajajo etilglukuronid (angl. *β -D-ethyl glucuronide*, EtG), etilsulfat (angl. *ethyl sulphate*, EtS), etilfosfat (angl. *ethyl phosphate*, EtP), fosfatidiletanol (angl. *phosphatidylethanol*, PEth) in etilni estri maščobnih kislin (angl. *fatty acid ethyl esters*, FAE) [7].

Nedavno uživanje alkohola lahko zaznamo v izdihanem zraku, z meritvijo koncentracije alkohola v krvi ali z neposrednimi biomarkerji za dokazovanje uživanja alkohola v krvi in urinu [5, 6]. V preteklosti so se za dokazovanje uživanja alkohola uporabljali predvsem posredni biomarkerji, ki ne merijo količine zaužitega alkohola ali njihovih metabolitov neposredno, temveč odražajo njegove fiziološke učinke na organe, predvsem jetra in druge biokemične procese v telesu. Med posredne biomarkerje spadajo gama-glutamilttransferaza (GGT), aspartat-aminotransferaza (AST), alanin-aminotransferaza (ALT), povprečni volumen eritrocitov (angl. *mean corpuscular volume*, MCV) in transferin s pomanjkanjem ogljikovih hidratov (angl. *carbohydrate-deficient transferrin*, CDT) [8].

Ti biomarkerji so uporabni za prepoznavanje oseb, ki dolgotrajno prekomerno uživajo alkohol, njihova občutljivost za prepoznavo oseb, ki zmerno uživajo alkohol, pa je omejena [9]. Prednost neposrednih biomarkerjev je v tem, da nastajajo le ob prisotnosti alkohola v organizmu, zato je zanje značilna manjša pogostost lažno pozitivnih rezultatov, ki zmanjšuje zanesljivost posrednih biomarkerjev. Poleg tega pa prepoznajo tudi zgolj občasno prekomerno uživanje alkohola. Med neposredne biomarkerje uživanja alkohola spadata PEth in EtG [8].

Fosfatidiletanol

PEth je atipičen fosfolipid, ki nastaja iz fosfatidilholina (angl. *phosphatidylcholine*, PC) v prisotnosti etanola. Encim fosfolipaza D (angl. *phospholipase D*, PLD) običajno katalizira hidrolizo PC, pri čemer nastane fosfatidna kislina. Ob prisotnosti etanola katalizira reakcijo transfosfatidilacije, pri kateri etanol sprejme fosfatidilno skupino in nastane fosfatidiletanol [10]. Opisanih je več kot 40 različnih oblik PEth, med katerimi je najpogostejši in klinično najpomembnejši PEth 16:0/18:1. Vgrajuje se v membrane eritrocitov in se ob nadaljnjem uživanju alkohola v njih postopoma kopiči. Iz telesa se izloča počasi, njegov razpolovni čas je dvofazen in znaša približno 3–10

dni. Glede na količino in vzorec uživanja alkohola je lahko PEth v krvi zaznaven še do 4 tedne po prenehanju pitja, zato omogoča oceno uživanja alkohola v daljšem časovnem obdobju [9].

Določanje fosfatidil etanola v krvi

PEth se določa v polni krvi, odvzeti v epruveto z antikoagulantom etilendiamintetraocetno kislino (angl. *ethylenediaminetetraacetic acid*, EDTA) ali v vzorcih posušene krvi na filtrirnem papirju (angl. *dried blood spot*, DBS). Pred analizo se iz vzorca z uporabo organskih topil ekstrahira PEth, pri čemer se kot notranji standard uporablja devterirana spojina. Analiza najpogosteje poteka s tekočinsko kromatografijo s tandemsko masno spektrometrijo (angl. *liquid chromatography-tandem mass spectrometry*, LC-MS/MS). PEth se z ultravisokotlačno tekočinsko kromatografijo loči od drugih komponent vzorca na koloni s stacionarno fazo C₁₈. Pri tem se uporablja ionizacija z elektrorazprševanjem v negativnem načinu, za določanje EtG pa metoda spremljanja izbranih reakcij [11]. Najpogosteje določeni homolog je PEth 16:0/18:1, ki ima najdaljšo razpolovno dobo in je pogosto edini homolog PEth, ki ga v klinični praksi določamo [12].

Prednosti in slabosti določanja fosfatidil etanola v krvi

Prednosti PEth pred drugimi posrednimi biomarkerji za ugotavljanje uživanja alkohola so predvsem njegova visoka specifičnost (> 90 %) in občutljivost (> 88 %), daljše obdobje zaznavnosti in objektivnost rezultata. PEth nastaja v prisotnosti etanola, zato je bolj neposredno povezan z uživanjem alkohola kot omenjeni posredni biomarkerji. Pomembna prednost je tudi ta, da jetrna bolezen ne vpliva na njegovo koncentracijo v krvi. Zaradi njegove visoke občutljivosti lahko zlasti pri ponavljajočem in prekomernem uživanju zaznamo nižje koncentracije, ki jih z določanjem drugih biomarkerjev ne bi mogli zaznati. Njegova dodatna prednost je tudi daljše obdobje zaznavnosti. Etanol se iz krvi izplavi

precej hitro, medtem ko PEth ostane v krvi zaznaven še več tednov po prenehanju uživanja. Z merjenjem PEth v krvi dobimo objektivni rezultat, ki ni odvisen od bolnikovega priklica in pripravljenosti, da bi priznal uživanje alkohola [9, 13, 14].

Kljub številnim prednostim ima PEth tudi nekatere omejitve, ki jih je treba upoštevati pri interpretaciji rezultatov PEth iz krvi. Na podlagi njegove koncentracije ni mogoče popolnoma natančno določiti zaužite količine alkohola, saj se povezuje med izmerjeno koncentracijo in količino zaužitega alkohola pri posameznikih precej razlikuje. Zaradi njegovega dolgega časovnega okna zaznavnosti na podlagi izmerjene vrednosti ni mogoče natančno določiti časa zaužitja alkohola. Kljub visoki občutljivosti lahko občasno uživanje manjših količin alkohola ostane pod mejo zaznavnosti, zato je možen lažno negativen rezultat. Ker PEth nastaja v membranah eritrocitov, lahko hemoliza povzroči nižje izmerjene vrednosti tega biomarkerja, nedavna transfuzija krvi pa lažno višje vrednosti tudi pri tistih osebah, ki alkohola niso uživale. Na interpretacijo rezultatov vpliva tudi variabilna razpolovna doba PEth, saj se njegova koncentracija pri različnih posameznikih zmanjšuje z različno hitrostjo. Ena od omejitev določanja PEth je tudi potreba po odvzemu krvi, ki je za razliko od odvzema urina, las ali nohtov bolj invaziven in za nekatere bolnike neprijeten poseg. Dodatno omejitev predstavljata dostopnost in cena analize, ki zahteva specializirane laboratorijske metode [9, 13, 14]. PEth torej predstavlja zelo zanesljiv biomarker prekomernega uživanja alkohola, če izmerjene rezultate pravilno interpretiramo ter ob tem upoštevamo tudi klinično oceno in druge metode za ocenjevanje vnosa alkohola [12].

Etilglukoronid

Etilglukuronid (EtG) je majhna, nehlapna, vodotopna molekula, ki je bila prvič odkrita leta 1993 v laseh [15]. Je neposredni metabolit etanola, ki nastane v jetrih z encimsko konjugacijo etanola z glukuronsko kislino, kar katalizira z membrano

mitohondrijev povezana UDP-glukuronoziltransferaza. Z urinom se izloči zelo majhen delež zaužitega etanola (<1 %) v obliki EtG in EtS. Ta dva metabolita je mogoče zaznati v različnih telesnih tekočinah in tkivih še dolgo po tem, ko je bil alkohol že izplavljen iz telesa. EtG se v praksi najpogosteje določa v urinu, vendar ga je mogoče določati tudi v polni krvi, kjer je zaznaven že v manj kot 45 minutah po zaužitju alkohola in vse do 36 ur, v serumu, laseh in nohtih [16, 17, 18]. V krvi in urinu je primeren za zaznavanje alkohola v kratkem časovnem obdobju po zaužitju. V keratinskih tkivih, kot so lasje in nohti, pa omogoča dolgotrajnejše spremljanje [19].

Določanje etilglukoronida v urinu

EtG v urinu (uEtG) je polarna, vodotopna spojina, zato je za njegovo analizo potrebna ustrezna priprava vzorca, ki zmanjša vpliv drugih sestavin urina na rezultat meritve [20, 21, 22]. Za učinkovito čiščenje vzorcev se lahko uporablja ekstrakcija na trdni fazi, redčenje vzorca in obarjanje beljakovin z organskimi topili, izbira postopka pa je odvisna od analitiške metode in zahtevane občutljivosti [23, 24, 25]. Alternativen pristop je analiza posušenih madežev urina na filtrirnem papirju (angl. *dried urine spot*, DUS), pri kateri se analit ekstrahira z metanolom ob uporabi ultrazvočne obdelave [20, 26]. Za določanje uEtG se v klinični praksi najpogosteje uporabljata LC-MS in LC-MS/MS, ki omogočata zanesljivo identifikacijo in kvantifikacijo ter sta primerni tudi za sodnomedicinske preiskave. Imunokemijski testi (angl. *enzyme immunoassay*, EIA), ki se uporabljajo predvsem za presejalno testiranje, lahko zaradi navzkrižne reaktivnosti z drugimi snovmi dajejo lažno pozitivne rezultate, zato je treba začetne pozitivne rezultate, ki so zgolj orientacijski, potrditi s kromatografsko metodo. Vzorce je potrebno čim hitreje dostaviti v laboratorij, do takrat pa jih je potrebno hraniti v hladilniku [16].

Časovno okno zaznavanja je odvisno od uporabljene mejne vrednosti in količine zaužitega alkohola [27]. uETG omogoča zaznavanje uživanja alkohola še več

ur do nekaj dni po tem, ko etanola v izdihanem zraku, krvi ali urinu ni več mogoče zaznati. V kontroliranih kliničnih študijah je običajno obdobje zaznavanja v urinu približno 24–72 ur, pri čemer se lahko po večjem zaužitju alkohola in ob uporabi nižjih mejnih vrednosti podaljša [28, 29, 30].

Prednosti in slabosti določanja etilglukoronida v urinu

uEtG je visoko občutljiv in specifičen biomarker za ugotavljanje nedavnega uživanja alkohola [31]. Zaradi enostavnega in neinvazivnega odvzema vzorca ter podaljšanega časovnega okna zaznavnosti v primerjavi z etanolom se pogosto uporablja za spremljanje uživanja alkohola in odkrivanje ponovnega uživanja po obdobju abstinence. Zaradi visoke občutljivosti omogoča zaznavanje že manjših količin zaužitega alkohola [32]. Prednost uEtG je v tem, da je tudi pri bolnikih z jetrnimi boleznimi občutljiv in specifičen kazalec zaznavanja zaužitega alkohola v obdobju zadnjih treh dni, ne glede na stopnjo resnosti jetrne bolezni [33].

Pomembna omejitev določanja uEtG je izbira mejne vrednosti, ki vpliva na občutljivost in specifičnost testa. Nižje mejne vrednosti omogočajo zaznavanje manjših količin zaužitega alkohola in podaljšajo obdobje zaznavanja, vendar lahko povečajo tveganje za lažno pozitivne rezultate. Nasprotno pa višje mejne vrednosti povečajo specifičnost, vendar lahko povzročijo, da manjše količine zaužitega alkohola ostanejo nezaznane. Občutljivost testa se zmanjšuje tudi z daljšanjem časa od zaužitega alkohola, zato negativen rezultat ne izključuje predhodnega uživanja [27, 34].

Mejna koncentracija EtG 100 ng/mL najverjetneje omogoča najboljše zaznavanje intenzivnega uživanja alkohola v obdobju zadnjih petih dni. V okoliščinah, kjer je nujno, da bi čim bolj zmanjšali število lažno pozitivnih rezultatov (npr. v sodno-medicinskih postopkih), se priporoča uporaba mejnih koncentracij 200 ng/mL ali več. V kliničnem in raziskovalnem okolju se za čim boljše zaznava-

nje intenzivnega uživanja alkohola priporoča mejna koncentracija 100 ng/mL [27].

Na podlagi koncentracij EtG v urinu prav tako ni mogoče razlikovati med epizodo intenzivnega uživanja alkohola v zadnjih nekaj dneh in majhnim vnosom alkohola nekaj ur pred odvzemom vzorca. V posameznih primerih so bili rezultati uEtG pozitivni tudi po uporabi ustnih vodíc, ki vsebujejo etanol, in visoko koncentriranih razkužil na osnovi etanola. Prav tako lahko zaužitje večjih količin brezalkoholnega piva povzroči pozitivne rezultate uEtG in EtS v urinu do 20 ur po zaužitju. Bolnike je zato pred testiranjem potrebno opozoriti na te možnosti in jih o teh stvareh tudi povprašati [16].

Pomembna omejitev je tudi ta, da je koncentracija EtG v urinu odvisna od diureze, zato lahko zaužitje večjih količin vode povzroči izrazito znižanje njegove koncentracije v urinu, kar lahko vodi do lažno negativnih rezultatov [16].

Določanje etilglukoronida v lasih

Določanje EtG v lasih (hEtG) običajno vključuje odvzem vzorca las z zadnjega zgornjega dela lasišča, pri čemer se najpogosteje analizira proksimalni tricentimetrski segment, ki približno odraža trimesečno obdobje rasti lasu. Za analizo se navadno uporabi 15–200 mg las [19]. Odvzeti vzorec se sprva opere, da se odstranijo zunanji kontaminanti, nato posuši in razreže na krajše segmente (0,1–0,3 cm) ali homogenizira z mletjem. EtG se nato ekstrahira, najpogosteje z destilirano vodo ob inkubaciji in/ali ultrazvočni obdelavi. Kot notranji standard se uporablja izotopsko označeni EtG. Kvantifikacija poteka z LC-MS/MS ali plinsko kromatografijo s tandemsko masno spektrometrijo (angl. *gas chromatography-tandem mass spectrometry*, GC-MS/MS). Rezultati se izražajo v pg/mg las [15].

Čeprav so osnovni koraki analize primerljivi, se laboratorijski protokoli razlikujejo glede postopkov pranja, homogenizacije, ekstrakcije in izbire analitske metode [19].

Po priporočilih mednarodnega strokovnega združenja za analizo drog in drugih substanc v človeških lasih (*Society of Hair Testing*, SoHT) koncentracija hEtG pod 5 pg/mg ne kaže na čezmerno uživanje alkohola, vrednosti med 5 in 30 pg/mg pa lahko kažejo na ponavljajoče se uživanje alkohola. Koncentracija nad 30 pg/mg močno podpira sum na kronično čezmerno uživanje alkohola. Pri posameznikih s pomembnimi sočasnimi boleznimi je potrebna previdnost, saj je lahko interpretacija teh mejnih vrednosti manj zanesljiva [19].

Prednosti in slabosti določanja etilglukoronida v lasih

Pomembna prednost hEtG je dolgo obdobje zaznavnosti, ki po aktualnih priporočilih SoHT omogoča zanesljivo kvantifikacijo za obdobje približno šestih mesecev. Poleg tega je odvzem vzorca neinvaziven, shranjevanje preprosto, rezultati pa niso odvisni od starosti, spola, indeksa telesne mase (ITM) ali naravne barve las, kar omogoča zanesljivejšo vrednotenje uživanja alkohola pri posameznikih z različnimi demografskimi in telesnimi lastnostmi [15]. hEtG ima visoko občutljivost (85 %) in specifičnost (97 %) pri zaznavanju čezmernega uživanja alkohola, tj. več kot 60 g alkohola na dan, ob upoštevanju mejne vrednosti 30 pg/mg v proksimalnem tricentimetrskem odseku las [15].

Kljub visoki specifičnosti ima določanje hEtG tudi nekaj omejitev, ki so v glavnem povezane s pomanjkanjem standardnih laboratorijskih postopkov, saj se metode pranja, mletja in ekstrakcije vzorcev med laboratoriji razlikujejo. To lahko vpliva na primerljivost rezultatov. Na izmerjeno koncentracijo vplivajo tudi predanalitski dejavniki, kot so postopek dekontaminacije, homogenizacija vzorca, uporabljeno ekstrakcijsko topilo in temperatura. Interpretacijo dodatno otežujejo različne mejne vrednosti, ki vodijo do lažno pozitivnih ali lažno negativnih rezultatov. Pomembno vlogo pri interpretaciji imajo tudi individualne lastnosti, kot so splošno zdravstveno stanje, zlasti ledvična bole-

zen, jetrna ciroza in sladkorna bolezen ter uporaba kozmetičnih izdelkov za lase, saj lahko vplivajo na izmerjeno vrednost. Zato je treba pri interpretaciji rezultatov upoštevati klinično stanja posameznika in podatke o morebitni obdelavi las [19]. Dolgotrajna izpostavljenost las parfumu na alkoholni osnovi lahko poveča koncentracijo hEtG in tako privede do lažno pozitivnih rezultatov [35]. Na rezultat lahko vpliva tudi dolgotrajen stik z vodo, zlasti pri plavanju v bazenih ali pogostem kopanju v kadi. Prav tako je pomembna pomanjkljivost, da negativen rezultat ne izključuje občasnega uživanja manjših količin alkohola, saj je občutljivost metode v tem primeru omejena. Rezultate je smiselno interpretirati v kombinaciji s kliničnimi podatki in določanjem drugih biomarkerjev, predvsem skupaj s PEth [15]. Raziskave so pokazale, da so njegove koncentracije višje v serumu kot v polni krvi. Zato je pri interpretaciji pomembno upoštevati tudi biološki vzorec uporabljen za analizo [18].

Določanje etilglukoronida v nohtih

EtG se v noht vgrajuje prek krvnega obtoka v predelu nohtne matice in nohtne posteljice pod nohtom. Odvzem vzorca nohtnega tkiva je neinvaziven postopek, vzorec pa je lažje pridobiti kot kri ali urin [36]. Tako kot pri analizi las je tudi za analizo nohtov potrebna le majhna količina vzorca, ki ga je mogoče hraniti pri sobni temperaturi [37]. Vzorec nohta pridobimo z odrezom njegovega distalnega dela. Priprava vzorcev za določanje EtG vključuje dekontaminacijo, sušenje, mletje, ekstrakcijo analita in čiščenje ekstrakta. EtG se določa z metodo LC-MS/MS in GC-MS/MS. Pri slednji je lahko pogosto potrebna derivatizacija, ki izboljša analitsko občutljivost [38, 39].

Povezava med koncentracijo EtG v nohtnem tkivu (nEtG) in vzorci uživanja alkohola kaže, da je analiza nohtov uporabna za ocenjevanje uživanja alkohola v daljšem časovnem obdobju. Časovno okno zaznavanja nEtG je približno 3–6 mesecev in je odvisno od hitrosti rasti nohta in dolžine analiziranega vzorca [36].

Koncentracija nEtG ima višjo občutljivost pri posameznikih s pogostejšim uživanjem alkohola kot pri tistih z nizko do zmerno stopnjo uživanja alkohola [40].

Mejne vrednosti za EtG še niso standardizirane. Cappelle idr. so predlagali preliminarne mejne vrednosti, pri čemer koncentracija nad 123 pg/mg kaže na kronično prekomerno uživanje alkohola, vrednosti med 59 in 123 pg/mg na zmerno uživanje alkohola, vrednosti pod 59 pg/mg pa na abstinenco. Berger idr. so predlagali drugačne mejne vrednosti, in sicer 56 pg/mg za opredelitev oseb z visokim tveganjem za prekomerno uživanje alkohola in 37 pg/mg za osebe s povečanim tveganjem. Vermeulen idr. so proučevali koncentracije nEtG pri osebah, ki so vsaj 6 mesecev abstinitale, in ugotovili, da koncentracija nEtG pod 7,6 pg/mg ne nasprotuje abstinenči. Najvišja koncentracija, ki so jo zaznali, je bila 23 pg/mg. Ti rezultati nakazujejo, da so prej predlagane mejne vrednosti za abstinenco (37 pg/mg, 59 pg/mg) morda previsoke [37].

Prednosti in slabosti določanja etilglukoronida v nohtih

Analiza nohtov ima v primerjavi z analizo las več prednosti. Nohti namreč rastejo počasneje kot lasje, in sicer nohti na rokah približno 3 mm na mesec, nohti na nogah pa 1 mm na mesec, medtem ko lasje na glavi zrastejo približno 1 cm na mesec. Zaradi počasnejše rasti nohtov se lahko EtG v njih intenzivneje kopiči, kar omogoča zaznavanje tudi nizkih koncentracij te snovi, na primer pri razlikovanju med osebami, ki alkohola ne uživajo, in tistimi, ki ga uživajo zmerno. Poleg tega lahko analiza nohtov predstavlja alternativo v primerih, ko vzorci las niso na voljo ali ko ni na voljo zadostne količine vzorca [39].

Kljub temu ima tudi analiza nohtov nekatere pomanjkljivosti. Mednje sodijo: nezadostna količina vzorca pri osebah, ki si grizejo nohte, prisotnost bolezni nohtov, kot so bakterijske ali glivične okužbe, ter možni vplivi lakiranja in čiščenja nohtov na rezultate analize [39].

KLINIČNA UPORABNOST

PEth in EtG sta pomembna neposredna biomarkerja za objektivno ugotavljanje in spremljanje uživanja alkohola. Njuna uporaba je posebej koristna, kadar podatki iz anamneze bolnikovega dejanskega uživanja alkohola ne odražajo zanesljivo, na primer zaradi nenamerne podcenjevanja količine ali nepripravljenosti za razkritje uživanja. Rezultati lahko dopolnijo klinično oceno in pomagajo pri prepoznavanju tveganega ali škodljivega uživanja alkohola, prav tako pa tudi pri spremljanju bolnikov, vključenih v zdravljenje zaradi prekomernega uživanja alkohola ali celo odvisnosti od alkohola.

Pomembna prednost omenjenih biomarkerjev je, da omogočata ocenjevanje uživanja alkohola v različnih časovnih obdobjih. PEth v krvi odraža predvsem uživanje v predhodnih nekaj tednih, medtem ko EtG v urinu omogoča zaznavanje nedavnega uživanja, predvsem v zadnjih 24–72 urah. Določanje EtG v lasih oziroma nohtih pa omogoča retrospektivno oceno uživanja v daljšem, večmesečnem obdobju. Sočasno določanje PEth in EtG je zato lahko koristno, kadar želimo pridobiti širši vpogled v vzorec uživanja alkohola ali preveriti skladnost rezultatov z bolnikovo anamnezo. Na primer, pozitiven EtG v urinu ob nizki koncentraciji PEth lahko kaže na nedavno uživanje, ki še ni povzročilo izrazitejšega porasta PEth. Pri tem je potrebno upoštevati različna časovna okna zaznavnosti obeh biomarkerjev [41].

EtG v urinu se pogosto uporablja pri spremljanju abstinence med zdravljenjem odvisnosti od alkohola, saj omogoča zaznavanje nedavnega uživanja tudi po tem, ko etanola v telesu ni več mogoče neposredno zaznati. PEth je zaradi daljšega obdobja zaznavnosti primernejši za spremljanje uživanja za obdobje zadnjih nekaj tednov. Večkratne meritve obeh biomarkerjev so koristne tudi za oceno uspešnosti zdravljenja in pri prepoznavi ponovnega uživanja alkohola. EtG v lasih in nohtih je uporaben predvsem takrat, ko je potrebna

retrospektivna ocena daljšega obdobja, vendar rezultati ne omogočajo natančne določitve količine ali časa zaužitja alkohola [28].

Pri interpretaciji rezultatov je vedno potrebno upoštevati uporabljeno metodo, mejne vrednosti, čas odvzema vzorca in vpliv drugih dejavnikov, ki povzročajo lažno višje ali lažno nižje izmerjene vrednosti. Pozitiven rezultat ne omogoča vedno zanesljive ocene količine zaužitega alkohola, negativen pa ne izključuje uživanja izven obdobja zaznavnosti. Biomarkerji zato ne morejo povsem nadomestiti anamneze in celostne klinične ocene,

temveč ju dopolnjujejo ter omogočajo objektivnejše spremljanje bolnika in ustrežnejše načrtovanje nadaljnje obravnave.

PRIMERJAVA NEPOSREDNIH BIOMARKERJEV ZA UGOTAVLJANJE UŽIVANJA ALKOHOLA

Tabela 1 povzema primerjavo glavnih značilnosti neposrednih biomarkerjev za ugotavljanje uživanja alkohola: časovno okno zaznavnosti, prednosti in omejitve biomarkerjev ter klinično uporabnost.

Tabela 1: Primerjava neposrednih biomarkerjev za ugotavljanje uživanja alkohola
Table 1: Comparison of direct biomarkers for the detection of alcohol consumption

Značilnosti	PEth	uEtG	hEtG	nEtG
Časovno okno zaznavnosti	Do 4 tedne	24–72 ur	Do 6 mesecev	3–6 mesecev
Glavne prednosti	Jetrna bolezen ne vpliva na izmerjeno vrednost. Dolgo okno zaznavnosti.	Neinvaziven odvzem. Jetrna bolezen ne vpliva na izmerjeno vrednost. Primeren za sledenje abstinence.	Neinvaziven odvzem. Preprosto shranjevanje. Ni vpliva starosti, spola, ITM, barve las.	Počasnejša rast nohtov pomeni večje kopičenje EtG. Primerno za določanje že nizkih zaužitih količin.
Glavne omejitve	Odvzem krvi z iglo. Ne definira natančne količine ali časa zaužitja alkohola. Hemoliza lahko povzroči lažno nižje vrednosti. Transfuzija lahko povzroči lažno višje vrednosti.	Etanol v ustnih vodicah, razkužilnih in brezalkoholnem pivu lahko povzroči lažno višje vrednosti. Odvisnost izmerjene koncentracije od mejne vrednosti.	Nestandardizirani laboratorijski postopki. Kozmetični postopki, parfumi na osnovi alkohola vplivajo na lažno višje vrednosti.	Ni primerno pri pogrizenih nohtih, boleznih nohtov. Vpliv lakiranja in čiščenja nohtov na rezultat. Manj standardizirane mejne vrednosti.
Klinična uporabnost	Objektivna ocena uživanja alkohola v predhodnih tednih. Spremljanje sprememb v uživanju in ocenjevanje uspešnosti zdravljenja. Pomoč pri prepoznavanju ponovnega uživanja alkohola.	Zaznavanje nedavnega uživanja alkohola (običajno v zadnjih 24–72 urah). Spremljanje abstinence med zdravljenjem odvisnosti od alkohola. Prepoznavanje nedavnega uživanja, če ga anamneza ne potrjuje.	Retrospektivna ocena uživanja alkohola v daljšem, večmesečnem obdobju. Dopolnilna ocena vzorca uživanja pri sumu na dolgotrajno čezmerno uživanje alkohola.	Dopolnilna retrospektivna ocena uživanja alkohola v daljšem obdobju, zlasti kadar je analiza las manj primerna.

ZAKLJUČEK

Objektivno ugotavljanje uživanja alkohola je pomembno za pravočasno prepoznavanje škodljivih vzorcev uživanja, ki lahko zgolj na podlagi anamneze ostanejo neprepoznani. Zanesljivejša ocena uživanja alkohola omogoča zgodnejše ukrepanje, ustreznejše načrtovanje obravnave in spremljanje sprememb v vzorcih uživanja ter tako prispeva k preprečevanju ali vsaj zmanjšanju resnosti zdravstvenih posledic, ki jih prekomerno uživanja alkohola povzroča.

Neposredna biomarkerja fosfatidiletanol (PEth) in etilglukuronid (EtG) predstavljata pomembno dopolnitev tradicionalnim metodam, saj omogočata objektivnejše vrednotenje uživanja alkohola v različnih časovnih obdobjih. PEth v krvi omogoča predvsem oceno uživanja v daljšem časovnem obdobju (do nekaj tednov), EtG v urinu zaznavanje kratkoročnega uživanja, določanje EtG v lasih in nohtih pa retrospektivno oceno v večmesečnem obdobju. Izbira ustreznega biomarkerja je zato odvisna predvsem od namena preiskave in obdobja, v katerem želimo oceniti uživanje alkohola.

Kljub visoki občutljivosti in specifičnosti biomarkerjev je treba pri interpretaciji rezultatov upoštevati omejitve posameznih metod, izbrane mejne vrednosti, čas odvzema vzorca in druge dejavnike, ki lahko vplivajo na izmerjeno vrednost. Posamezna meritev ne omogoča vedno zanesljive ocene količine zaužitega alkohola ali natančne opredelitve vzorca uživanja, negativen rezultat pa uživanja zunaj časovnega okna zaznavnosti ne izključuje. Biomarkerji zato ne nadomeščajo anamneze in celostne klinične ocene, temveč ju dopolnjujejo. Njihova premišljena uporaba omogoča zanesljivejšo vrednotenje uživanja alkohola in predstavlja pomembno podporo pri prepoznavanju oseb, ki potrebujejo nadaljnjo obravnavo.

Za širšo in zanesljivejšo rabo biomarkerjev v klinični praksi so potrebne nadaljne raziskave o diagnostični vrednosti biomarkerjev, poenotenje analitskih metod in določanja mejnih vrednosti ter jasna opredelitev uporabnosti posameznega biomarkerja v različnih kliničnih okoliščinah. S tem bi izboljšali primerljivost rezultatov med različnimi laboratoriji in dodatno prispevali k zanesljivosti vrednotenja uživanja alkohola.

Literatura

- Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet Lond Engl*. 2018;391:1513–23. doi: 10.1016/S0140-6736(18)30134-X
- Díaz LA, König D, Weber S, et al. Management of alcohol use disorder: a gastroenterology and hepatology-focused perspective. *Lancet Gastroenterol Hepatol*. 2025;10:475–90. doi: 10.1016/S2468-1253(24)00380-7
- Davis CG, Thake J, Vilhena N. Social desirability biases in self-reported alcohol consumption and harms. *Addict Behav*. 2010;35:302–11. doi: 10.1016/j.addbeh.2009.11.001
- Gmel G, Daepfen JB. Recall bias for seven-day recall measurement of alcohol consumption among emergency department patients: implications for case-crossover designs. *J Stud Alcohol Drugs*. 2007;68:303–10. doi: 10.15288/jsad.2007.68.303
- Schröck A, Wurst FM, Thon N, et al. Assessing phosphatidylethanol (PEth) levels reflecting different drinking habits in comparison to the alcohol use disorders identification test - C (AUDIT-C). *Drug Alcohol Depend*. 2017;178:80–6. doi: 10.1016/j.drugalcdep.2017.04.026
- Peterson K. Biomarkers for alcohol use and abuse—a summary. *Alcohol Res Health J Natl Inst Alcohol Abuse Alcohol*. :28:30–7.
- Morini L, Politi L, Groppi A, et al. Determination of ethyl glucuronide in hair samples by liquid chromatography/electrospray tandem mass spectrometry. *J Mass Spectrom JMS*. 2006;41:34–42. doi: 10.1002/jms.943
- Kane JC, Chirayil P, Pawar R, et al. Measuring alcohol consumption with biomarkers in intervention studies: A scoping review. *Alcohol Clin Exp Res*. 2025;49:1843–54. doi: 10.1111/acer.70114
- Perilli M, Toselli F, Franceschetto L, et al. Phosphatidylethanol (PEth) in Blood as a Marker of Unhealthy Alcohol Use: A Systematic Review with Novel Molecular Insights. *Int J Mol Sci*. 2023;24. doi: 10.3390/ijms241512175
- Maenhout TM, De Buyzere ML, Delanghe JR. Non-oxidative ethanol metabolites as a measure of alcohol intake. *Clin Chim Acta Int J Clin Chem*. 2013;415:322–9. doi: 10.1016/j.cca.2012.11.014
- Berg T, Eliassen E, Jørgenrud B, et al. Determination of phosphatidylethanol 16:0/18:1 in whole blood by 96-well supported liquid extraction and UHPLC-MS/MS. *J Clin Lab Anal*. 2019;33:e22631–e22631. doi: 10.1002/jcla.22631
- Hahn JA, Murnane PM, Vittinghoff E, et al. Factors associated with phosphatidylethanol (PEth) sensitivity for detecting unhealthy alcohol use: An individual patient data meta-analysis. *Alcohol Clin Exp Res*. 2021;45:1166–87. doi: 10.1111/acer.14611
- Viel G, Boscolo-Berto R, Cecchetto G, et al. Phosphatidylethanol in blood as a marker of chronic alcohol use: a systematic review and meta-analysis. *Int J Mol Sci*. 2012;13:14788–812. doi: 10.3390/ijms131114788
- Helander A, Hansson T. The alcohol biomarker phosphatidylethanol (PEth) - test performance and experiences from routine analysis and external quality assessment. *Scand J Clin Lab Invest*. 2023;83:424–31. doi: 10.1080/00365513.2023.2253734
- Biondi A, Freni F, Carelli C, et al. Ethyl glucuronide hair testing: A review. *Forensic Sci Int*. 2019;300:106–19. doi: 10.1016/j.forsciint.2019.05.004
- Andresen-Streichert H, Müller A, Glahn A, et al. Alcohol Biomarkers in Clinical and Forensic Contexts. *Dtsch Arzteblatt Int*. 2018;115:309–15. doi: 10.3238/arztebl.2018.0309
- Landberg R. Can Urinary Ethyl Glucuronide Be Used as a Biomarker of Habitual Alcohol Consumption? *J Nutr*. 2019;149:2077–8. doi: 10.1093/jn/nxz201
- Walsham NE, Sherwood RA. Ethyl glucuronide. *Ann Clin Biochem*. 2012;49:110–7. doi: 10.1258/acb.2011.011115
- Triolo V, Spanò M, Buscemi R, et al. EtG Quantification in Hair and Different Reference Cut-Offs in Relation to Various Pathologies: A Scoping Review. *Toxics*. 2022;10. doi: 10.3390/toxics10110682
- Wang H, Zhang Y, Fan E, et al. A novel fast-dried urine spot-based method for the analysis of EtS and EtG in urine by liquid chromatography tandem mass spectrometry. *J Chromatogr B*. 2021;1171:122642–122642. doi: 10.1016/j.jchromb.2021.122642
- Ghosh S, Jain R, Singh S, et al. A simplified approach for determination of urinary ethyl glucuronide by gas chromatography–mass spectrometry. *J Anal Sci Technol*. 2021;12:35–35. doi: 10.1186/s40543-021-00290-6
- Simms P. B-161 Liquid chromatography/mass spectrometry analysis of ethyl glucuronide and ethyl sulfate using a perfluorophenyl stationary phase. *Clin Chem*. 2024;70:hvae106.521-hvae106.521. doi: 10.1093/clinchem/hvae106.521
- Zheng Y, Helander A. Solid-Phase Extraction Procedure for Ethyl Glucuronide in Urine. *J Anal Toxicol*. 2008;32:778–81. doi: 10.1093/jat/32.9.778
- Janda I, Alt A. Improvement of ethyl glucuronide determination in human urine and serum samples by solid-phase extraction. *J Chromatogr B Biomed Sci App*. 2001;758:229–34. doi: 10.1016/S0378-4347(01)00186-4
- Santhosh SR, Sampath S, Gupta A, et al. Development and validation of LCMS method for determination of Ethyl Glucuronide (EtG) in urine. *Med J Armed Forces India*. 2022;78:316–21. doi: 10.1016/j.mjafi.2021.03.010
- Hernández Redondo A, Körber C, König S, et al. Inhibition of bacterial degradation of EtG by collection as dried urine spots (DUS). *Anal Bioanal Chem*. 2012;402:2417–24. doi: 10.1007/s00216-011-5687-7
- McDonnell MG, Skalksky J, Leickly E, et al. Using ethyl glucuronide in urine to detect light and heavy drinking in alcohol dependent outpatients. *Drug Alcohol Depend*. 2015;157:184–7. doi: 10.1016/j.drugalcdep.2015.10.004
- van de Luitgaarden IAT, Beulens JWJ, Schrieks IC, et al. Urinary Ethyl Glucuronide Can Be Used as a Biomarker of Habitual Alcohol Consumption in the General Population. *J Nutr*. 2019;149:2199–205. doi: 10.1093/jn/nxz146
- Jones AW. Brief history of the alcohol biomarkers CDT, EtG, EtS, 5-HTOL, and PEth. *Drug Test Anal*. 2024;16:570–87. doi: 10.1002/dta.3584
- Meredith LR, Kirkland AE, Green R, et al. Strong concordance and correlation between direct alcohol biomarkers and alcohol self-report among youth with variable drinking patterns. *Drug Alcohol Depend*. 2025;274:112734–112734. doi: 10.1016/j.drugalcdep.2025.112734
- Tawiah KD, Riley SB, Budelier MM. Biomarkers and Clinical Laboratory Detection of Acute and Chronic Ethanol Use. *Clin Chem*. 2022;68:635–45. doi: 10.1093/clinchem/hvac004
- Palmer RB. A review of the use of ethyl glucuronide as a marker for ethanol consumption in forensic and clinical medicine. *Semin Diagn Pathol*. 2009;26:18–27. doi: 10.1053/j.semdp.2008.12.005
- Stewart SH, Koch DG, Burgess DM, et al. Sensitivity and specificity of urinary ethyl glucuronide and ethyl sulfate in liver disease patients. *Alcohol Clin Exp Res*. 2013;37:150–5. doi: 10.1111/j.1530-0277.2012.01855.x
- Jatlow PI, Agro A, Wu R, et al. Ethyl glucuronide and ethyl sulfate assays in clinical trials, interpretation, and limitations: results of a dose ranging alcohol challenge study and 2 clinical trials. *Alcohol Clin Exp Res*. 2014;38:2056–65. doi: 10.1111/acer.12407

- 35 Morini L, Sempio C, Moretti M. Ethyl Glucuronide in Hair (hEtG) after Exposure to Alcohol-based Perfumes. *Curr Pharm Biotechnol.* 2018;19:175–9. doi: 10.2174/1389201019666180405164208
- 36 Keten A, Zeren C, Arslan MM, *et al.* Determination of ethyl glucuronide in fingernails by LC/MS-MS. *Romanian J Leg Med.* 2013;21:67–72. doi: 10.4323/rjlm.2013.67
- 37 Vermeulen L, van Nuijs ALN, Crunelle CL, *et al.* Ethyl glucuronide and alcohol abstinence: A correlation study in hair and fingernails to establish a cut-off value in fingernails for teetotalers. *Forensic Sci Int.* 2022;335:111278–111278. doi: 10.1016/j.forsciint.2022.111278
- 38 Jones J, Jones M, Plate C, *et al.* Liquid Chromatography-Tandem Mass Spectrometry Assay to Detect Ethyl Glucuronide in Human Fingernail: Comparison to Hair and Gender Differences. *Am J Anal Chem.* 2012;3:83–91. doi: 10.4236/ajac.2012.31012
- 39 Cappelle D, Neels H, Yegles M, *et al.* Ethyl glucuronide in nails: method validation, influence of decontamination and pulverization, and particle size evaluation. *Forensic Toxicol.* 2016;34:158–65. doi: 10.1007/s11419-015-0302-9
- 40 Morie KP, Gilstad-Hayden K, Martino S, *et al.* Sensitivity, specificity, and discordance with self-report of nail sample testing for alcohol and cannabis. *Drug Alcohol Depend.* 2024;261:111358–111358. doi: 10.1016/j.drugalcdep.2024.111358
- 41 Reisfield GM, Teitelbaum SA, Opie SO, *et al.* The roles of phosphatidylethanol, ethyl glucuronide, and ethyl sulfate in identifying alcohol consumption among participants in professionals health programs. *Drug Test Anal.* 2020;12:1102–8. doi: 10.1002/dta.2809