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Adverse Outcomes of Anesthetic Interventions in Cirrhotic Patients: A Systematic Review

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Abstract
Objectives: To assess and summarize the adverse outcomes associated with anesthetic interventions in cirrhotic patients. **Methods:** A total of 543 pertinent publications were found after a comprehensive search across four databases. 50 full-text publications were examined after duplicates were eliminated using Rayyan QCRI and relevance was checked; seven studies finally satisfied the requirements for inclusion. **Results:** We included seven studies with a total of 12,267patients, and more than half of them 6918 (56.4%) were females.This review highlights that remimazolam and propofol are safer anesthetic options for cirrhotic patients, reducing risks like hypotension, hypoxia, and prolonged recovery. In contrast, midazolam worsens encephalopathy and causes more hemodynamic instability. Rare complications, including hypoxia and cardiovascular events, were reported with benzodiazepines, narcotics, and general anesthesia. Tailored anesthetic strategies are essential to minimize risks in this high-risk population.**Conclusion:** Remimazolam and propofol are safer anesthetic options for cirrhotic patients, reducing hemodynamic and respiratory risks, while midazolam and general anesthesia pose higher risks, especially in advanced liver dysfunction. Individualized strategies, careful monitoring, and further research are essential to improving perioperative care in this vulnerable population.
Keywords; Cirrhotic patients, Anesthesia, Perioperative complications, Sedation, Liver dysfunction,Systematic review.

Introduction

The lobular and vascular architecture of the liver is destroyed in cirrhosis, an advanced type of fibrosis [1]. Portal hypertension brought on by the advancement of liver illness can result in consequences including gastric antral vascular ectasia, portal hypertensive gastropathy, and esophagogastricvarices [2–4]. It can be difficult to select the right sedative for these individuals, who frequently have upper gastrointestinal endoscopies for diagnostic or therapeutic purposes. Even when administered by skilled professionals, sedation poses higher risks in this group of patients with underlying liver disease and its complications because of baseline hemodynamics, drug metabolism and interactions, and an elevated likelihood of adverse events. Anesthesiologists, endoscopists, or registered nurses can deliver mild to moderate sedation, which is the recommended dosage for elective endoscopies in patients with cirrhosis [5].

Among the medications frequently used for GI endoscopic sedation include propofol, fentanyl, and midazolam. Etomidate, ketamine, and dexmedetomidine are rarely used. The majority of these sedatives compromise the circulatory system and decrease myocardial contractility. The exceptions to this rule, etomidate and ketamine, are generally administered to individuals who have a weakened cardiovascular system. Patients with severe cirrhosis had a much longer elimination half-life of midazolam and lower clearance [6], which is independent of albumin or bilirubin levels in the blood. Midazolam used for GI endoscopy may cause psychomotor impairment that lasts for up to six hours following treatment. Plasma levels return to normal after liver transplantation, and midazolam's effects are not prolonged [7]. Complications from intra-procedure sedation should be minimal with proper titration.

Cirrhotic patients undergoing surgical procedures are at significantly elevated risk due to compromised liver function, altered hemodynamics, and coagulopathies. Anesthetic interventions in this population can exacerbate these vulnerabilities, leading to adverse outcomes such as hepatic decompensation, encephalopathy, prolonged recovery, and mortality. Understanding the risks and identifying best practices in anesthetic care is crucial to optimize perioperative outcomes and guide clinicians in making evidence-based decisions. A systematic review consolidating existing research will provide a comprehensive analysis of the relationship between anesthesia and adverse outcomes in cirrhotic patients, addressing a critical knowledge gap in perioperative care.The objective of this systematic review is to assess and summarize the adverse outcomes associated with anesthetic interventions in cirrhotic patients.

Methods

Search strategy

The systematic review was done based on the PRISMA and GATHER criteria. An exhaustive search was made to identify studies related to the adverse outcomes associated with anesthetic interventions in cirrhotic patients. The

reviewers searched four electronic databases: SCOPUS, Web of Science, Cochrane, and PubMed. After removing any duplicates, we uploaded to Rayyan every abstract and title we could locate using electronic searches. We included studies published within the last 5 years (2020-2024). The full texts of the study texts that fulfilled the inclusion criteria according to their abstract or title were retrieved for a detailed analysis. Two independent reviewers assessed the appropriateness of the extracted publications and reviewed inconsistencies.

Study population—selection

The PICO (Population, Intervention, Comparator, and Outcome) factors were implemented as inclusion criteria for our review: (i) Population: Cirrhotic patients undergoing surgical procedures, (ii) Intervention: Different types of anesthetic interventions, (iii) Comparator: Non-cirrhotic patients undergoing similar procedures with anesthesia, (iv) Outcomes: Adverse outcomes, including perioperativeand postoperative complications.

Data extraction

Data from studies that satisfied the inclusion requirements were extracted by two objective reviewers using a predetermined and uniform methodology. The following information was retrieved and recorded: (i) First author (ii) Year of publication, (iii) Study design, (iv) Participants' number, (v) Age, (vi) Gender, (vii) Anesthetic drugs, (viii) Surgical procedure, (ix) Adverse outcomes.

Quality review

The reviewers evaluated the methodological quality using the New Castle-Ottawa Quality Assessment Scale for Cohort Studies, which was modified for Cross-Sectional Studies and takes into account three categories (Selection, Comparability, and Outcomes) [8]. A Newcastle-Ottawa form score of ≥7 was regarded as excellent quality, a score of 5–6 as moderate quality, and a score of 0–4 as low quality [9].

Results

The specified search strategy yielded 543 publications **(Figure 1).** After removing duplicates (n = 290), 253 trials were evaluated based on title and abstract. Of these, 81 failed to satisfy eligibility criteria, leaving just 50 full-text articles for comprehensive review. A total of 7 satisfied the requirements for eligibility with evidence synthesis for analysis.

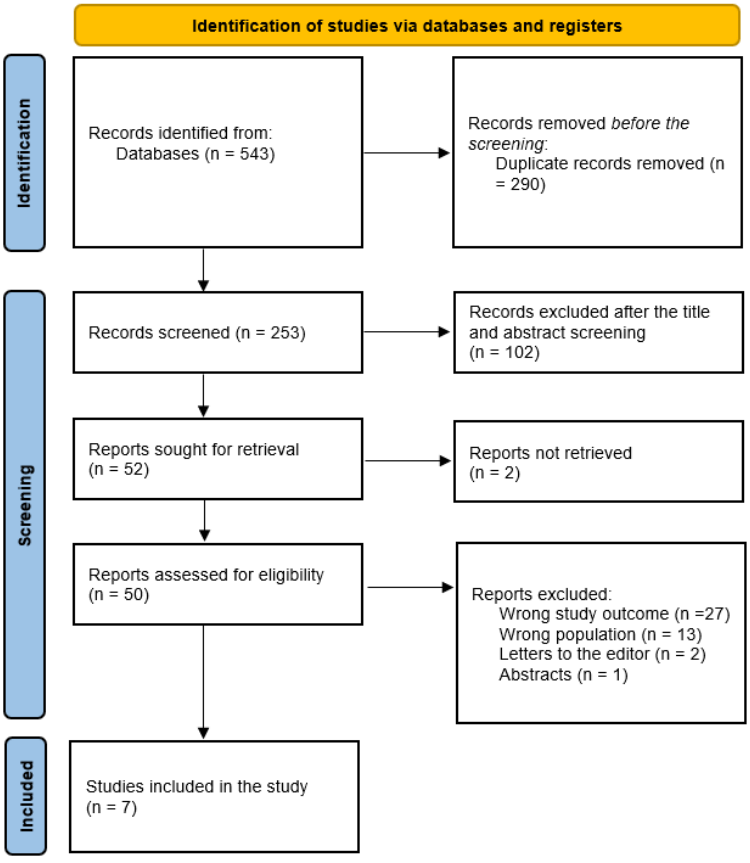

Figure (1): PRISMA flowchart [10].

Sociodemographic and clinical outcomes

We included seven studies with a total of 12,267patients, and more than half of them 6918 (56.4%) were females. Regarding study designs, three studies were RCTs [11, 14, 15], three were retrospective cohorts [12, 16, 17], and one was a cross-sectional [13]. Three studies were implemented in China [11, 15, 16], two in the USA [12, 13], one in Korea [14], and one in Egypt [17].

Remimazolam

Two studies [11, 15], evaluated the use of remimazolam in cirrhotic patients undergoing procedures such as EVL and EGD. The results consistently demonstrated that remimazolam was associated with a reduction in common adverse outcomes, including low SpO2, hypotension, body movement, and respiratory depression. The findings suggest that remimazolam provides a safer sedation profile for cirrhotic patients compared to other agents, likely due to its rapid metabolism and hemodynamic stability.

Benzodiazepines and Narcotics

In the retrospective cohort study [12], the use of benzodiazepines and narcotics during EGD led to various complications, albeit at a low rate of 0.6%. Adverse outcomes included perforation, laryngospasm, bleeding, hypoxia, and bradycardia. Though rare, these events highlight the need for caution in cirrhotic patients where even minimal hypoxia or cardiovascular instability can precipitate further hepatic decompensation.

Etomidate and Propofol

Notably, etomidate was associated with maintaining stable hepatic function, as it did not exacerbate overt or subclinical hepatic encephalopathy [14]. On the other hand, another study compared midazolam and propofol and found that while midazolamworsened subclinical encephalopathy and caused more pronounced hypotension and tachycardia, propofol offered a better safety profile. Patients in the propofol group experienced shorter induction, procedure, and recovery times, underscoring its advantages for sedation in cirrhotic patients [17].

Midazolam

Cirrhotic patients who received midazolam experienced exacerbation of subclinical encephalopathy, alongside more frequent hypotension and tachycardia. These findings point to midazolam’s potential risks in patients with liver dysfunction, as its prolonged metabolism can exacerbate neurological and hemodynamic instability [17].

Table (1): Outcome measures of the included studies.

Study ID	Study design	Country	Sociodemographic	Anesthetic drug	Surgical procedure	Adverse outcomes	NOS
Shi et al., 2022 [11]	RCT	China	N: 76 Mean age: 51.6 Females: 42 (55.3%)	Remimazolamtosilate	EVL	Remimazolam tosilate reduced the likelihood of side effects such low SpO2 and hypotension.	NA*
Edelson et al., 2020 [12]	Retrospective cohort	USA	N: 2618 Mean age: 55.3 Females: 944 (36%)	Benzodiazepine and narcotics	EGD	Among the side effects were perforation (1), laryngospasm (1), bleeding (5), hypoxia (7), and bradycardia (1). Similar rates of 0.6% were observed for colonoscopy, ERCP, and EGD.	6
Lieber et al., 2020 [13]	Cross-sectional	USA	N: 9007 Mean age: 58 Females: 5616 (62.4%)	NS	Endoscopic procedures	Overall, complications from endoscopic treatments in cirrhosis are uncommon. The majority of serious problems were cardiac in nature and were linked to more ill individuals receiving general anesthesia.	7
Jung et al., 2020 [14]	RCT	Korea	N: 126 Mean age: 54.5 Females: 37 (29.4%)	Etomidate and Propofol	EGD	Sedation based on etomidate does not worsen overt or subclinical hepatic encephalopathy.	NA
Cao et al., 2022	RCT	China	N: 148 Mean age: 47.6 Females: 87	Remimazolamtosilate	EGD	Body movement, hypotension, and respiratory depression	NA

[15]			(58.7%)			were less common in patients treated with remimazolam.	
Wang et al., 2021 [16]	Retrospective cohort	China	N: 232 Mean age: 57 Females: 162 (69.8%)	NS	EGD	Of 40 complications (17.2%) from 2015 to 2019, 87.5% were postprocedural (pain, nausea, vomiting). Serious complications (3.4%) were mostly cardiovascular (87.5%). Patients with complications had longer postoperative stays (P<0.05).	8
Hamed et al., 2023 [17]	Retrospective cohort	Egypt	N: 60 Age range: 17-65 Females: 30 (50%)	Midazolam& propofol	EGD	Subclinical encephalopathy is made worse by midazolam. Compared to the propofol group, the midazolam group experienced more pronounced hypotension and tachycardia during the surgery. Propofol-treated subjects had reduced induction, procedure, and recovery times.	7

Discussion

The findings of this systematic review highlight the critical role of anesthetic selection in cirrhotic patients to minimize adverse outcomes.Two studies in this review [11, 15] found that remimazolam reduced adverse outcomes such as hypoxia, hypotension, and respiratory depression in cirrhotic patients undergoing EVL and EGD, highlighting its safer sedation profile due to rapid metabolism and hemodynamic stability.A more recent benzodiazepine with structural similarities to midazolam, remimazolam exhibits remifentanil's metabolic profile and undergoes organ-independent ester hydrolysis. As a result, cirrhotic patients are more likely to exhibit propofol-like wakefulness than midazolam-like wakefulness. Remimazolam may therefore be more effective in treating cirrhosis than other medications in its class [18].**Onoda*et al.*** reported that Remimazolam is a suitable anesthetic option for liver cirrhosis patients in order to stabilize circulation and induce rapid waking. As remimazolam's use grows among patients with more severe cirrhosis and as blood medication concentrations are monitored, it is envisaged that its safety will be verified in the future [19].

This review found a 0.6% complication rate with benzodiazepines and narcotics during EGD, including perforation, hypoxia, and bradycardia. Although rare, these events warrant caution as even minor hypoxia or instability can worsen hepatic decompensation in cirrhotic patients.**Goudra*et al.*** reported that patients with cirrhosis who had started using benzodiazepines three to ten days prior were much more likely to experience their first episode of HE. This extra risk was not present in cirrhosis patients who had been using benzodiazepines for more than 28 days or for just one or two days [20].

We found that Etomidate maintained stable hepatic function without worsening encephalopathy [14]. In contrast, midazolam worsened subclinical encephalopathy and caused more hypotension and tachycardia, while propofol showed a better safety profile with shorter induction, procedure, and recovery times, making it preferable for sedation in cirrhotic patients [17].Many of propofol's characteristics make it unsuitable for patients with severe cirrhosis. It is advised to lower the dosage in these individuals due to their greater susceptibility to the sedative and cardiorespiratory depressive effects of propofol [20]. However, **Suh*et al.*** [21] did not find respiratory depression or clinically significant hypotension in a trial of 20 liver cirrhosis patients and 20 control persons undergoing upper GI endoscopy. Even in cirrhotic patients with mild hepatic encephalopathy, there was no post-procedural decline in psychomotor function, despite the fact that psychomotor performance was more compromised in these individuals.

Our review found that midazolam worsened subclinical encephalopathy and increased hypotension and tachycardia in cirrhotic patients, highlighting its risks due to prolonged metabolism and potential for neurological and hemodynamic instability [17].**Khamaysi*et al.*** reported that patients with liver illness metabolize midazolam more slowly, with a higher volume of distribution and less protein binding. In patients with cirrhosis, midazolam is thought to increase the risk of hepatic encephalopathy. There are numerous benefits to using ketamine in cirrhosis patients [22].

These findings have essential clinical implications for anesthetic management in cirrhotic patients. First, remimazolam and propofol should be recommended as first-line agents when sedation is required for diagnostic or therapeutic procedures due to their better safety profile with minimal side effects. Second, midazolam should be strictly avoided or used with great caution in patients at risk of either encephalopathy or hemodynamic instability.

Clinicians should also avoid the use of benzodiazepines and narcotics, utilizing close intraoperative monitoring for the early detection of hypoxia, bradycardia, or bleeding. In patients who require general anesthesia, detailed preoperative cardiac risk assessment and optimized monitoring are paramount in the prevention of complications. An individualized approach based on the severity of liver disease, hemodynamic stability, and metabolic capacity is essential to ensure safer perioperative outcomes.

Strengths

The strengths of this systematic review include the fact that evidence has been synthesized from several studies; it provides a state-of-the-art analysis of the safety and adverse effects of different anesthetic agents in cirrhotic patients. Inclusion of various study designs such as randomized controlled trials, retrospective cohorts, and cross-sectional studies enhances generalizability. Furthermore, the mainstay anesthetic agents to be compared are remimazolam, propofol, and midazolam, which would provide practical insights that may inform clinical practice in improving patient outcomes.

Limitations

The following are some limitations despite its strengths. The studies were disparate on sample size, anesthetic protocol, and the core outcome variables measured; therefore, the heterogeneity limits the possibilities for direct comparison. Moreover, there are those studies where anesthetic drugs were not mentioned; hence, conclusions cannot be made in this regard. Moreover, the absence of long-term follow-up in most studies restricts the evaluation of delayed complications or outcomes, which are important in cirrhotic patients. Further, the geographic

concentration of studies in regions such as China and the USA may limit global applicability because of differences in clinical practices and healthcare systems.

Conclusion

Therefore, remimazolam and propofol could be considered safer anesthetic choices in cirrhotic patients, based on the reduced risk of both hemodynamic instability and respiratory complications. In contrast, midazolam and general anesthesia may entail a higher risk, particularly in those with advanced liver dysfunction. An individualized approach to anesthetic strategy, closely managed intraoperative monitoring, and assessment of specific risks will help to minimize the possibility of adverse outcomes in this fragile population. Future research with standardized protocols and extended follow-up is needed to further refine clinical guidelines and enhance perioperative care for cirrhotic patients.

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