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The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS, World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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Hypophosphatemia as a prognostic tool for post-hepatectomy liver failure: A systematic review

Romualdas Riauka, Povilas Ignatavicius, Giedrius Barauskas

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Abstract

BACKGROUND

Post-hepatectomy liver failure (PHLF) is one of the main causes of postoperative mortality and is challenging to predict early in patients after liver resection. Some studies suggest that the postoperative serum phosphorus might predict outcomes in these patients.

AIM

To perform a systematic literature review on hypophosphatemia and evaluate it as a prognostic factor for PHLF and overall morbidity.

METHODS

This systematic review was performed according to preferred reporting items for systematic reviews and meta-analyses statement. A study protocol for the review was registered in the International Prospective Register of Systematic Reviews database. PubMed, Cochrane and Lippincott Williams & Wilkins databases were systematically searched up to March 31, 2022 for studies analyzing postoperative hypophosphatemia as a prognostic factor for PHLF, overall postoperative morbidity and liver regeneration. The quality assessment of the included cohort studies was performed according to the Newcastle-Ottawa Scale.

RESULTS

After final assessment, nine studies (eight retrospective and one prospective cohort study) with 1677 patients were included in the systematic review. All selected studies scored ≥ 6 points according to the Newcastle-Ottawa Scale. Cutoff values of hypophosphatemia varied from < 1 mg/dL to ≤ 2.5 mg/dL in selected studies with ≤ 2.5 mg/dL being the most used defining value. Five studies analyzed PHLF, while the remaining four analyzed overall complications as a main outcome associated with hypophosphatemia. Only two of the selected studies analyzed postoperative liver regeneration, with reported better postoperative liver regeneration in cases of postoperative hypophosphatemia. In three studies hypophosphatemia was associated with better postoperative

outcomes, while six studies revealed hypophosphatemia as a predictive factor for worse patient outcomes.

CONCLUSION

Changes of the postoperative serum phosphorus level might be useful for predicting outcomes after liver resection. However, routine measurement of perioperative serum phosphorus levels remains questionable and should be evaluated individually.

Key Words: Hypophosphatemia; Post-hepatectomy liver failure; Liver regeneration; Serum phosphorus; Literature review

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Core Tip: A systematic literature review on hypophosphatemia and its value as a prognostic factor for post-hepatectomy liver failure and overall morbidity after liver surgery was performed. In three of nine included studies hypophosphatemia was associated with better postoperative outcomes, while six studies revealed hypophosphatemia as a predictive factor for worse patient outcomes. Data show that postoperative hypophosphatemia and changes of postoperative serum phosphorus might be used as a predictor after liver surgery. However, to be implemented in clinical practice as routine measurement more studies and data are needed.

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INTRODUCTION

Post-hepatectomy liver failure (PHLF) is a severe and lethal complication occurring in patients after partial liver resection and defined by derangement of liver function, coagulopathy, high lactate and encephalopathy[1]. Incidence of PHLF varies from 1% to 32% with reported perioperative mortality up to 60%[2,3]. PHLF is a significant complication and one of the main causes of mortality in patients after liver resection even with advancing surgical techniques and perioperative management[4,5]. A wide variety of preoperative predictive factors, such as patient-related (male sex, older age, obesity), hepatic parenchyma-related (cirrhosis, fibrosis, steatosis, preoperative chemotherapy, cholestasis), surgery-related (high blood loss, extended liver resection, prolonged inflow occlusion and operating time) and postoperative course-related (hemorrhage, infections), might contribute to PHLF[4,6,7]. Despite various scoring systems for standardizing PHLF and predicting postoperative morbidity and mortality, early identification of patients, who will develop PHLF remains challenging[8].

Regenerative potential of hepatocytes and the compensatory capacity of the functional liver remnant allow resection of up to 80% of the healthy liver[9,10]. Patients at risk of PHLF do not exhibit a normal regenerative response and may present with early disorders in normal metabolic responses, such as failure to utilize serum phosphorus postoperatively[11,12]. Consequently, absence of a decrease in postoperative serum phosphorus might be an early predictive factor of PHLF. Organic phosphate is part of several important biological processes such as signal transduction, energy transfer and formation of high-energy bonds and is critical to multiple metabolic processes[13]. Blood phosphate levels are regulated by various organs such as bone, parathyroid glands, small intestine, kidneys and liver, thus the pathophysiology of postoperative hypophosphatemia is multifactorial[14,15].

According to Woodard *et al*[16] liver tissue contains approximately 0.3% phosphorus by weight. Low serum phosphate levels after major liver resection might be associated with removal of liver mass containing phosphorus, resulting in blood phosphate movement into the hepatocytes and, subsequently, better liver regeneration[17,18]. Some studies suggested that postoperative serum hypophosphatemia might predict better outcomes in patients with acute liver failure[19,20]. Absence of hypophosphatemia after major liver resections might help identify patients with an increased chance of PHLF.

Several studies present contradictory results. Postoperative hypophosphatemia was reported to be associated with a higher risk of postoperative complications, thus refuting the previous statements[21-23]. It is hypothesized that liver regeneration after major hepatectomy results in serum phosphorus replenishing intracellular phosphorus levels needed for ATP synthesis and further regeneration processes. Therefore, low serum phosphorus levels impair liver regeneration, resulting in liver

dysfunction and failure[24,25]. Therefore, data on postoperative hypophosphatemia as a prognostic factor for PHLF are yet to be systemically analyzed. Our aim was to perform a systematic literature review of hypophosphatemia as a prognostic tool for PHLF and overall morbidity.

MATERIALS AND METHODS

This systematic review was performed according to the preferred reporting items for systematic reviews and meta-analyses statement[26]. A study protocol for the review was registered in the International Prospective Register of Systematic Reviews database: CRD42020197717.

Search strategies

PubMed, Cochrane, Lippincott Williams & Wilkins and *Reference Citation Analysis* databases were searched up to March 31, 2022. Our search terms included: (hypophosphatemia OR phosphorus) AND (hepatectomy OR liver resection) AND (post-operative hepatic insufficiency OR mortality OR complications OR liver failure OR liver insufficiency). After checking titles and abstracts, inappropriate studies were excluded. The remaining full-text articles were reviewed carefully. Additionally, reference lists of selected articles were reviewed for eligible studies.

Study selection

Inclusion criteria for selected studies were: (1) Studies written in English language; and (2) Studies analyzing postoperative hypophosphatemia as a prognostic factor for PHLF, overall postoperative morbidity and liver regeneration (patients after different types of liver resections, including living-donor liver donation). Exclusion criteria were as follows: (1) Abstracts, case reports, editorials, letters, systematic reviews and meta-analyses; (2) Studies with incomplete data for further analysis (studies with no reported postoperative complications or phosphorus, studies analyzing postoperative hypophosphatemia in liver transplant recipients); (3) Duplicate studies; and (4) Studies in languages other than English.

Data extraction and quality assessment

Selected studies were evaluated by two investigators independently, and necessary data was extracted including name of the first author, year of publication, type of study, number of patients included in the study, study population (type of surgery performed), postoperative phosphorus, main and secondary outcomes (PHLF, overall postoperative morbidity and liver regeneration) and their correlation with postoperative hypophosphatemia. In cases of disagreement, differences in opinion were resolved by a third author.

The quality assessment of the included cohort studies was performed according to the Newcastle-Ottawa Scale[27]. Evaluation ranged from 0 to 9 points, and studies with a Newcastle-Ottawa Scale score of ≥ 6 were considered as high quality. Due to heterogeneity of included studies and analyzed populations meta-analysis and subgroup analysis was not conducted.

RESULTS

PubMed, Cochrane, and Lippincott Williams & Wilkins databases were searched, and 264 articles were initially retrieved. After removing 45 duplicates, 219 articles were left for screening. One hundred ninety-six articles were removed after screening titles and abstracts due to inappropriate topics, leaving 23 full-text articles for further assessment. After final assessment, nine studies (eight retrospective and one prospective cohort study) with 1677 patients were included in the systematic review (Table 1). The selection process is summarized by preferred reporting items for systematic reviews and meta-analyses flow diagram (Figure 1).

The majority of included studies were characterized by wide variation (inconsistency) of the extent of performed liver resections[11,21-23,28-30]. Indications for liver surgery [colorectal cancer liver metastases, metastatic neuroendocrine tumors, cholangiocarcinoma, hepatocellular carcinoma, sarcoma, metastases of other primary tumors and benign diseases (hemangiomas, cysts, primary sclerosing cholangitis)] were also different. Patients with local ablation of liver tumors were included in one study [21]. Hypophosphatemia after living-donor liver donation was analyzed in 2 studies[24,31]. Quality of the selected studies was evaluated by two investigators independently according to the Newcastle-Ottawa Scale. All selected studies scored ≥ 6 points with the of the studies (6) scoring 7 points, making them eligible to be included in further analysis (Table 1).

Postoperative outcomes

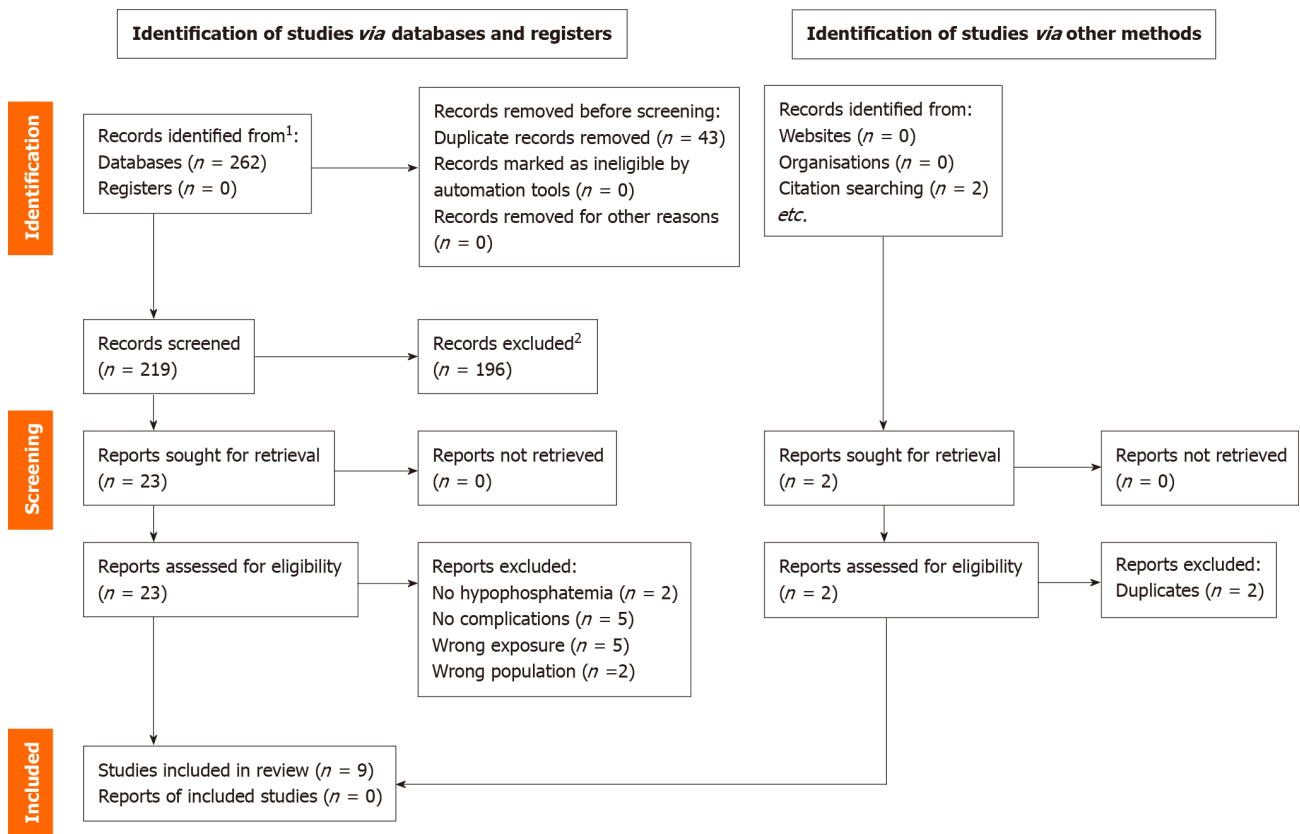
PHLF as the main outcome associated with postoperative hypophosphatemia was analyzed in five out of nine included studies[11,24,29-31]. Liver failure in selected studies was defined using 50-50 criteria

Table 1 Characteristics of included studies

Ref.	Study type	NOS	N	Study population	Cutoff phosphorus level	Main outcomes	Results	Conclusions
George <i>et al</i> [28], 1992	Retrospective	6	44	Liver resections	≤ 2.5 mg/dL	Postoperative complications	Profound HP group had higher frequency rate of postoperative complications ($P < 0.005$)	Hypophosphatemia increased risk of postoperative complications
Buell <i>et al</i> [21], 1998	Retrospective	6	35	Liver resections and cryosurgery	< 2.5 mg/dL	Postoperative complications	More complications in HP group (80% vs 28%; $P < 0.05$)	Hypophosphatemia increased risk of postoperative complications
Giovannini <i>et al</i> [22], 2002	Retrospective	7	59	Liver resections	≤ 2.5 mg/dL	Postoperative complications	HP (< 1.5 mg/dL) associated with increase in rate of complications ($P < 0.001$)	Hypophosphatemia increased risk of postoperative complications
Smyrniotis <i>et al</i> [23], 2003	Prospective	7	30	Liver resections	< 1.5 mg/dL	Postoperative complications	Patients with HP (< 1.5 mg/dL) had more complications	Hypophosphatemia increased risk of postoperative complications
Yuan <i>et al</i> [24], 2011	Retrospective	6	132	LDLT	< 1 mg/dL	Liver insufficiency	MV binary logistic regression: Postoperative nadir serum phosphorus ($P = 0.01$) was independently related to hepatic functional impairment ($\beta = -5.927$, odds ratio 0.003; 95%CI: 0.000-0.239). Postoperative nadir of serum phosphorus < 1 mg/dL ($P = 0.006$, AUC = 0.731) led to more severe hepatic dysfunction	Hypophosphatemia increased risk of postoperative liver insufficiency
Squires <i>et al</i> [11], 2014	Retrospective	7	719	Liver resections	< 2.4 mg/dL	Liver insufficiency	UV: Patients with POD2 phosphorus > 2.4 demonstrated a significantly increased risk of PHLF ($P = 0.020$). MV: POD2 phosphorus > 2.4 mg/dL remained independently associated with a significantly increased risk of PHLF (HR = 1.78; 95%CI: 1.02-3.17; $P = 0.048$)	Absence of postoperative hypophosphatemia increased risk of postoperative complications and liver insufficiency
Hallet <i>et al</i> [29], 2016	Retrospective	7	402	Liver resections	≤ 2.01 mg/dL	Liver insufficiency	More patients with HP recovered from LI compared to those with NP (90.9% vs 65.0%, $P = 0.03$)	Postoperative hypophosphatemia associated with better recovery from PHLF
Margonis <i>et al</i> [30], 2016	Retrospective	7	95	Liver resections	≤ 2.4 mg/dL	Liver insufficiency	LI was lower in patients with HP ($P = 0.01$). MV analysis: Normal/high serum phosphorus on POD2 (HR = 3.24, 95%CI: 1.23-8.56; $P = 0.02$) remained independently associated with a worse OS	Postoperative hypophosphatemia associated with better OS, better liver regeneration and lower rate of liver insufficiency
Serrano <i>et al</i> [31], 2019	Retrospective	7	161	LDLT	≤ 2.5 mg/dL	Liver insufficiency	LI 1.77 mg/dL vs no LI 2.01 mg/dL for no LI cohort at a median of 1.6 d (38 h) postoperatively ($P = 0.003$). ROC postoperative phosphate levels through the first 38 h best predicted LI (sensitivity, 90%; specificity, 55.6%; positive predictive value, 11.8%; negative predictive value, 98.8%; AUC, 0.731)	Hypophosphatemia increased risk of postoperative liver insufficiency

AUC: Area under the receiver operating characteristic curve; CI: Confidence interval; HP: Hypophosphatemia; HR: Hazards ratio; LDLT: Living donor liver transplantation; LI: Liver insufficiency; MV: Multivariate; NP: Normophosphatemia; OS: Overall survival; PHLF: Post-hepatectomy liver failure; POD: Postoperative day; NOS: Newcastle-Ottawa Scale; ROC: Receiver operating characteristic; UV: Univariate.

introduced by Balzan *et al*[8] [prothrombin time < 50% and serum bilirubin > 50 μmol/L on postoperative day 5 (the 50-50 criteria)] or Mullen *et al*[32] (peak postoperative serum bilirubin > 7.0 mg/dL). In the four remaining studies, general postoperative complications (intraabdominal or



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Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram for new systematic reviews, which included searches of databases, registers and other sources. ¹PubMed, Cochrane, Lippincott Williams & Wilkins and Reference Citation Analysis databases. ²Recording excluded due to wrong topic, wrong language, unsuitable title, abstracts and case reports.

gastrointestinal bleeding, intraabdominal abscess, pneumonia, pleural effusion, pancreatitis, biliary fistula, neurological disorders, etc) with no or inadequate data on liver failure were analyzed[21-23,28]. Only two of the included studies analyzed serum phosphorus levels in relation to postoperative liver regeneration[29,30]. The extensive analysis of the included studies is presented in Table 1.

Cutoff values of hypophosphatemia varied from < 1 mg/dL to ≤ 2.5 mg/dL in selected studies with ≤ 2.5 mg/dL being the most used defining value (3 studies[22,28,31]). Only four of the included studies utilized hypophosphatemia values based on previous studies[11,28-30]. Phosphate concentration in the majority of the selected studies was measured daily starting with postoperative day 1 and was measured up to 10 d postoperatively with days 1, 2 and 3 after the operation being the most popular. In two studies the timing of serum phosphorus measurements was not reported[24,29].

DISCUSSION

This is the first systematic review including 1677 patients and analyzing postoperative serum phosphorus levels in correlation with PHLF and general surgical complications. In our systematic review we found that changes in postoperative serum phosphorus concentration may be useful for predicting outcomes of patients after extensive liver resections. However, each case and result need to be analyzed individually.

One of the first published studies on the topic reported that patients with more severe hypophosphatemia experienced a significantly higher rate of postoperative complications compared to patients with milder levels of phosphorus decrease[28]. Similar results were reported by Buell *et al*[21] analyzing clinical implications of hypophosphatemia following major hepatic resection or cryosurgery for liver tumors. The incidence of surgery-related complications was greater in patients with hypophosphatemia compared to patients without phosphorus decrease. Interestingly, hypophosphatemia did not increase complication rates or intensive care and hospital stay in patients undergoing cryotherapy. Two other studies by Giovannini *et al*[22] and Smyrniotis *et al*[23] reported similar outcomes. Patients with severe hypophosphatemia developed more complications and experienced a longer intensive care stay compared with patients with milder hypophosphatemia levels.

Similarly, Yuan *et al*[24] reported postoperative serum phosphorus nadir was independently associated with severe hepatic dysfunction. Authors of the study hypothesized that low serum phosphorus levels may be responsible for impaired intracellular regeneration processes resulting in further hepatic dysfunction. Hypophosphatemia as a predictive factor for PHLF was reported in a recent study by Serrano *et al*[31]. Patients with liver failure had significantly lower serum phosphorus levels at a median 38 h after operation.

In contrast, Squires *et al*[11], Hallet *et al*[29] and Margonis *et al*[30] revealed that patients with an absence of postoperative hypophosphatemia were more likely to experience higher rates of complications, liver insufficiency and even worse overall survival. Additionally, Hallet *et al*[29] and Margonis *et al*[30] reported better recovery from PHLF in patients with hypophosphatemia compared to patients with normophosphatemia. Only two of the selected studies (Hallet *et al*[29] and Margonis *et al*[30]) analyzed liver regeneration and reported better postoperative liver regeneration in cases of postoperative hypophosphatemia. The association between liver regeneration and postoperative serum hypophosphatemia relates to high energy consumption during the hepatocyte regeneration processes. Serum phosphorus is primarily used to foster liver recovery processes, such as DNA synthesis, reaching its maximum during the first 72 h after liver resection; however, it takes about 7 d for bone phosphorus to be mobilized into the blood[13,29,30,33].

Moreover, according to Margonis *et al*[30], patients who developed hyperphosphatemia after surgery had a worse overall survival, a higher risk of death and a worse liver regeneration index reaching up to 7 mo after liver surgery with exact mechanisms still uncertain. It is of interest to mention, that the latter three studies advocating the idea of a positive influence of hypophosphatemia on liver regeneration were published in the last 5 years and analyzed more than 70% ($n = 1216$) of patients from all included studies ($n = 1677$).

By analyzing the proposed mechanisms of phosphorus influence, it becomes evident that both hypotheses are based on the fact that phosphorus is needed to foster regenerative response. The difference is in the details. The first theory emphasizes the failure of cells to utilize phosphorus, and the second theory proposes that there is a lack of phosphorus to be utilized. Data on the dynamics of phosphorus concentrations in the pre- and postoperative periods could help understand the meaning of hypophosphatemia. Unfortunately, only two of the included studies provided data on preoperative phosphorus levels[22,24].

Phosphate is an essential element, necessary in a number of physiological processes such as skeletal mineralization and development, nucleotide structuring, membrane composition, *etc*[34,35]. Most phosphorus (85%) in the human body is found in the skeleton and maintained through the bone-kidney-intestine homeostatic network[36]. The outcome of this homeostatic network is a dynamic balance between urinary phosphate losses, intestinal phosphate absorption and reabsorption from bones, regulated by parathyroid hormone, fibroblast growth factor 23 and vitamin D.

The main reasons of non-surgery related hypophosphatemia are redistribution of phosphorus from extracellular fluids into cells, decreased intestinal absorption, high renal phosphate excretion and decreased proximal reabsorption with reduced activation of vitamin D[37]. For many years, increased liver regeneration and associated metabolic processes were thought to be the main reason of surgery-related hypophosphatemia. However, some authors have suggested that the severity of postoperative hypophosphatemia may not depend on just the extent of serum phosphorus uptake by the regenerating liver[13]. Studies by Salem *et al*[38] and Nafidi *et al*[39] revealed that phosphate renal loss was a more credible cause of postoperative hypophosphatemia than phosphorus consumption by the regenerating liver in their patients. Nomura *et al*[40] reported that liver surgery-related hypophosphatemia and hyperphosphaturia were associated with abnormal urinary nicotinamide metabolism in the liver and kidneys. The results were drawn from *in vitro* studies with opossum kidney cells and an animal model. However, exact mechanisms and factors of renal phosphaturia are yet to be investigated, analyzed and adapted for clinical use. Further studies are needed to better understand homeostasis of phosphorus to optimize patient outcomes.

The present systematic review has several limitations. First, only nine studies with a relatively small number of patients were eligible for inclusion in this systematic review. Second, eight out of nine included studies were of a retrospective design with a potential source of bias, while only one was a prospective cohort study. Differences between size of the investigated groups, different phosphorus cutoff values, the extent of liver resection not clearly defined, varying primary and secondary outcomes, varying statistical methods and phosphorus measurement days and intervals were other factors further contributing to increased heterogeneity. Finally, due to high heterogeneity between included studies there were not enough data to perform the appropriate meta-analysis.

CONCLUSION

We present the first systematic review analyzing postoperative serum phosphorus correlation with PHLF and general surgical complications. Changes in postoperative serum phosphorus concentrations may be useful for predicting outcomes of patients after extensive liver resections. However, it is

inconclusive whether the incidence or absence of post-hepatectomy hypophosphatemia is related to a better postoperative outcome. In our opinion, routine measurement of perioperative serum phosphorus levels remains questionable, and results should be evaluated individually to prevent PHLF and reduce overall liver surgery-related patient morbidity.

ARTICLE HIGHLIGHTS

Research background

Post-hepatectomy liver failure (PHLF) is a severe and serious complication occurring after high-volume liver resections and presenting with high perioperative mortality rates. There are contradictory results regarding serum phosphorus association with postoperative outcomes. Changes in serum phosphorus levels might predict development of PHLF and improve its treatment results.

Research motivation

Data of serum phosphorus level changes as a prognostic tool for PHLF is scarce and needs to be systematically analyzed.

Research objectives

To perform the first systematic review analyzing hypophosphatemia as a prognostic tool for PHLF and general complications.

Research methods

Study protocol for the review was registered in the International Prospective Register of Systematic Reviews database (D42020197717). This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses guidelines. PubMed, Cochrane and Lippincott Williams & Wilkins databases were searched up to March 31, 2022 using relevant search terms.

Research results

After thorough research, nine studies with 1677 patients were included in the systematic review. The majority of the included studies were retrospective. However, due to high heterogeneity between included studies there were not enough data to perform appropriate the meta-analysis.

Research conclusions

Changes of postoperative serum phosphorus concentration may be useful for predicting outcomes of patients after extensive liver resections. However, the decision to measure and interpret results needs to be considered individually with routine phosphorus level measurements, and its benefits remain questionable.

Research perspectives

Further high volume, non-randomized studies are needed to better analyze postoperative hypophosphatemia as a predictive factor for PHLF and general surgical outcomes.

FOOTNOTES

Author contributions: Riauka R, Ignatavicius P and Barauskas G contributed to study design and conception, data collection, analysis and interpretation and writing the draft of the manuscript; and all authors read and approved the published version of the manuscript.

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