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

Riauka R *et al.* Hypophosphatemia and PHLF

## **Abstract**

### **BACKGROUND**

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

### **AIM**

To perform 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 (PRISMA) 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 31<sup>st</sup> of March 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 Newcastle-Ottawa Scale (NOS).

### **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  $\geq 6$  points according to NOS. Cut-off values of hypophosphatemia varied from  $< 1$  mg/dL to  $\leq 2.5$  mg/dL in selected studies with  $\leq 2.5$  mg/dL being the most used defining value. Five studies analyzed PHLF, while remaining four analyzed overall complications as main outcome associated with hypophosphatemia. Only two of the selected studies analyzed postoperative liver regeneration, with reported better

postoperative liver regeneration in case of postoperative hypophosphatemia. In three studies hypophosphatemia was associated with better postoperative outcomes, while six studies revealed hypophosphatemia as predictive factor for worse patient outcomes.

## CONCLUSION

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

**Key Words:** Hypophosphatemia; Post-hepatectomy liver failure; Liver regeneration

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**Core Tip:** Systematic literature review on hypophosphatemia and evaluation of it 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 predictive factor for worse patient outcomes. Data show that postoperative hypophosphatemia and changes of postoperative serum phosphorus value might be used as predictor after liver surgery. However, to be implemented in the daily practice as routine measurement still more studies and data is needed.

## INTRODUCTION

Post-hepatectomy liver failure (PHLF) is severe and lethal complication occurring in patients after partial liver resection and defined by derangement of liver function, coagulopathy, high lactate and encephalopathy<sup>[1]</sup>. Incidence of PHLF varies from 1% to 32% with reported perioperative mortality up to 60%<sup>[2,3]</sup>. PHLF is significant

complication and one of the main causes of mortality in patients after liver resection even with advancing surgical techniques and perioperative management<sup>[4,5]</sup>. Wide variety of preoperative predictive factors such as: Patient related (male sex, older age, obesity), hepatic parenchyma related (cirrhosis, fibrosis, steatosis, pre-operative 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<sup>[4,6,7]</sup>. Despite various scoring systems for standardizing PHLF and predicting postoperative morbidity and mortality, early identification of patients, who will develop PHLF remains challenging<sup>[8]</sup>.

<sup>3</sup> Regenerative potential of hepatocytes and the compensatory capacity of functional liver remnant allow the resection up to 80% of healthy liver<sup>[9,10]</sup>. Patients at risk of PHLF do not exhibit normal regenerative response and may present with early disorders in normal metabolic responses, such as failure to utilize serum phosphorus postoperatively<sup>[11,12]</sup>. Consequently, absence of decrease in postoperative serum phosphorus values might be an early predictive factor of PHLF. Organic phosphate is part of several important biological processes such as signal transduction, energy transfer, formation of high-energy bonds and is critical to multiple metabolic processes<sup>[13]</sup>. 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<sup>[14,15]</sup>. According to Woodard and White<sup>[16]</sup> 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<sup>[17,18]</sup>. Some studies suggested that postoperative serum hypophosphatemia might predict better outcomes in patients with acute liver failure<sup>[19,20]</sup>. Absence of hypophosphatemia after major liver resections might help us to identify patients with increased chance of PHLF. Several studies present contradictory results – postoperative hypophosphatemia was reported to be associated with higher risk of postoperative complications, thus refuting the previous

statements<sup>[21-23]</sup>. 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<sup>[24,25]</sup>. Therefore, data on postoperative hypophosphatemia as a prognostic factor for PHLF are yet to be systemically analyzed. Our aim was to perform systematic literature review of hypophosphatemia as a prognostic tool for PHLF and overall morbidity.

## **MATERIALS AND METHODS**

This systematic review was performed according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement<sup>[26]</sup>. A study protocol for the review was registered in the International prospective register of systematic reviews database: CRD42020197717. We also cited high-quality articles in *Reference Citation Analysis* (<https://www.referencecitationanalysis.com>).

### ***Search strategies***

PubMed, Cochrane and Lippincott Williams & Wilkins databases were searched up to 31st of March 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. 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 value; 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: 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 value, main and secondary outcomes (PHLF, overall postoperative morbidity, and liver regeneration) and their correlation with postoperative hypophosphatemia. In case of disagreement, differences in opinion were resolved by a third author.

The quality assessment of the included cohort studies was performed according to Newcastle-Ottawa Scale (NOS)<sup>[27]</sup>. Evaluation ranged from 0 to 9 points and studies with NOS score of  $\geq 6$  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 left for screening. One hundred ninety-six (196) of these 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 in PRISMA flow diagram (Figure 1).

Majority of included studies (7<sup>[11,21-23,28-30]</sup>) were characterized by wide variation (inconsistency) in extent of performed liver resections. Indications for liver surgery (colorectal cancer liver metastases, metastatic neuroendocrine tumors, cholangiocarcinoma, hepatocellular carcinoma, sarcoma, metastases of other primary tumors, benign diseases (hemangiomas, cysts, primary sclerosing cholangitis) were also different. Patients with local ablation of liver tumors were included in one study<sup>[21]</sup>. Hypophosphatemia after living-donor liver donation was analyzed in 2 studies<sup>[24,31]</sup>. Quality of the selected studies was evaluated by two investigators independently according to NOS. All selected studies scored  $\geq 6$  points with majority of the studies (6) scoring 7 points, this way 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<sup>[11,24,29-31]</sup>. Liver failure in selected studies was defined using 50-50 criteria introduced by Balzan *et al*<sup>[8]</sup> [Prothrombin time  $< 50\%$  and serum bilirubin  $> 50 \mu\text{mol/L}$  on postoperative day 5 (the 50-50 criteria)] or Mullen *et al*<sup>[32]</sup> (peak postoperative serum bilirubin  $> 7.0 \text{ mg/dL}$ ). In four remaining studies general postoperative complications (intraabdominal or gastrointestinal bleeding, intraabdominal abscess, pneumonia, pleural effusion, pancreatitis, biliary fistula, neurological disorders and *etc.*) with no or inadequate data on liver failure were analyzed<sup>[21-23,28]</sup>. Only two of the included studies analyzed serum phosphorus level relation with postoperative liver regeneration<sup>[29,30]</sup>. The extensive analysis of the included studies is presented in Table 1.

Cut-off values of hypophosphatemia varied from  $< 1 \text{ mg/dL}$  to  $\leq 2.5 \text{ mg/dL}$  in selected studies with  $\leq 2.5 \text{ mg/dL}$  being the most used defining value (3 studies<sup>[22,28,31]</sup>). Only four of the included studies utilized hypophosphatemia values based on previous studies<sup>[11,28-30]</sup>. Phosphate concentration in 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<sup>[24,29]</sup>.

## **DISCUSSION**

This is the first systematic review, including 1677 patients and analyzing postoperative serum phosphorus correlation with PHLF and general surgical complications. In our systematic review we found out, that changes of postoperative serum phosphorus concentration may be useful 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 significantly higher rate of postoperative complications compared to patients with milder levels of phosphorus decrease<sup>[28]</sup>. Similar results were reported by Buell *et al*<sup>[21]</sup> analyzing clinical implications of hypophosphatemia following major hepatic resection or cryosurgery for liver tumors. 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*<sup>[22]</sup> and Smyrniotis *et al*<sup>[23]</sup> reported similar outcomes - patients with severe hypophosphatemia developed more complications and experienced longer intensive care stay compared with patients with milder hypophosphatemia levels. In concert go results of the study by Yuan *et al*<sup>[24]</sup> reporting postoperative serum phosphorus nadir was independently associated with severe hepatic dysfunction. Authors of the study hypothesize 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*<sup>[31]</sup>. Patients with liver failure had significantly lower serum phosphorus levels at median 38 h after operation. On the contrary studies by Squires *et al*<sup>[11]</sup>, Hallet *et al*<sup>[29]</sup> and Margonis *et al*<sup>[30]</sup> revealed that patients with absence of postoperative hypophosphatemia were more likely to

experience higher rate of complications, liver insufficiency and even worse overall survival. Additionally, Hallet *et al*<sup>[29]</sup> and Margonis *et al*<sup>[30]</sup> reported better recovery from PHLF in patients with hypophosphatemia compared to patients with normophosphatemia. Only two of the selected studies (Hallet *et al*<sup>[29]</sup> and Margonis *et al*<sup>[30]</sup>) analyzed liver regeneration, with reported better postoperative liver regeneration in case of postoperative hypophosphatemia. Association of liver regeneration and postoperative serum hypophosphatemia relates to high energy consuming hepatocyte regeneration processes. Serum phosphorus is primarily used to foster liver recovery processes, such as DNA synthesis, with its maximum reaching during first 72 h after liver resection; however, it takes about 7 d for bone phosphorus to be mobilized into the blood<sup>[13,29,30,33]</sup>. Moreover, according to Margonis *et al*<sup>[30]</sup>, patients who developed hyperphosphatemia after surgery had worse overall survival, higher risk of death and worse liver regeneration index reaching up to 7 mo after liver surgery with exact mechanisms still being uncertain. It is of interest to mention, that the latter 3 studies advocating the idea of positive influence of hypophosphatemia on liver regeneration are published during the last 5 years and are analyzing more than 70% ( $n = 1216$ ) of patients from all included studies ( $n = 1677$ ). 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 - first theory emphasizes failure of cells to utilize phosphorus, whereas the other - lack of phosphorus to be utilized. Possibly data on dynamics of phosphorus concentrations in pre- and postoperative periods could be of help understanding the meaning of hypophosphatemia. Unfortunately, only two of the included studies provide data on preoperative phosphorus levels<sup>[22,24]</sup>.

Phosphate is essential element, necessary in number of physiological processes such as skeletal mineralization and development, nucleotide structuring, membrane composition and etc<sup>[34,35]</sup>. Most of human body phosphorus (85%) is found in skeleton and maintained through bone-kidney-intestine homeostatic network<sup>[36]</sup>. 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. 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<sup>[37]</sup>. For many years, increased liver regeneration and associated metabolic processes were thought to be main reason of surgery related hypophosphatemia. However, some authors question it by indicating that severity of postoperative hypophosphatemia may depend not only on the extent of serum phosphorus uptake by regenerating liver<sup>[13]</sup>. Studies by Salem and Tray<sup>[38]</sup> and Nafidi *et al*<sup>[39]</sup> revealed that phosphate renal loss was more credible cause of postoperative hypophosphatemia than phosphorus consumption by regenerating liver in their patients. Nomura *et al*<sup>[40]</sup> has reported that liver surgery related hypophosphatemia and hyperphosphaturia were associated with abnormal urinary nicotinamide metabolism in liver and kidney. The results were drawn from *in-vitro* studies with opossum kidney cells and 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. Firstly, only nine studies with relatively small number of patients were eligible for inclusion in this systematic review. Secondly, eight out of nine included studies were of retrospective design with potential source of bias, while only one was a prospective cohort study. Difference between size of investigated groups, different phosphorus cut-off values, not clearly defined extent of liver resection, 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 appropriate meta-analysis.

## **CONCLUSION**

We present the first systematic review analyzing postoperative serum phosphorus correlation with PHLF and general surgical complications. Changes of postoperative serum phosphorus concentration may be useful predicting outcomes of patients after extensive liver resections. However, there are mixed opinions and results whether incidence or absence of post-hepatectomy hypophosphatemia is related to better postoperative outcomes. In our opinion, routine measurement of perioperative serum phosphorus level 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 severe and serious complication, occurring after high-volume liver resections and presenting with high perioperative mortality rates. There are contradictory results regarding serum phosphorus value association with postoperative outcomes. Changes in serum phosphorus value 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 systemically analyzed.

#### ***Research objectives***

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

#### ***Research methods***

Study protocol for the review was registered in 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 31<sup>st</sup> of March 2022 using relevant search terms.

### ***Research results***

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

### ***Research conclusions***

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

### ***Research perspectives***

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

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