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Retrospective Study

Hyponatremia is associated with more severe biliary disease

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Abstract**BACKGROUND**

Sodium level is an important clinical predictor of complex biliary disease. Hyponatremia has been observed in conjunction with biliary disease, however the nature of this association remains unclear.

AIM

To investigate the association between serum sodium and severe biliary disease.

METHODS

Of 920 patients with gallstone disease treated at the SFVA Hospital from 1989-2019 were studied. We conducted multivariate analyses of correlation between sodium level and biliary disease severity, the presence/location of biliary bacteria, and other factors. Minimum sodium level pre-intervention was collected. Gallstones, bile, and blood (as relevant) were cultured. Illness severity was characterized: (1) None (no infectious manifestations); (2) Systemic inflammatory response syndrome; (3) Severe illness (gangrenous cholecystitis, cholangitis, necrotizing pancreatitis); and (4) Multiple organ dysfunction syndrome (bacteremia, hypotension, organ failure). Comorbidity was defined using the Charlson Comorbidity Index (CCI).

RESULTS

Decreased sodium level significantly correlated with worsening illness severity, ascending bacterial infection, gangrenous changes, elevated CCI score, increasing age, male sex, and glucose. On multivariate analysis, all factors, except age, gender and glucose, independently correlated with sodium level and factors were additive.

CONCLUSION

This unique study is the first to explore, with such granularity, the relationship between biliary disease and sodium. No prior studies have examined specific culture and clinical data. It illustrates an inverse, independent correlation

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between illness severity and sodium. Culture data demonstrate that sodium decreases as infection ascends from gallstone colonization to bactibilia to bacteremia. Patient comorbidity and gangrenous changes also independently correlate with sodium on multivariate analysis. Sodium level is an important clinical indicator of disease severity for patients with biliary disease.

Key words: Hyponatremia; Biliary disease; Cholecystitis; Cholangitis; Sodium; Sepsis

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Core tip: This unique study is the first to explore, with such granularity, the relationship between biliary disease and sodium. No prior studies have examined specific culture and clinical data. It demonstrates an inverse, independent correlation between illness severity and sodium. Culture data demonstrate that sodium decreases as infection ascends from gallstone colonization to bactibilia to bacteremia. Patient comorbidity and gangrenous changes also independently correlate with sodium on multivariate analysis. Sodium level is an important clinical indicator of disease severity for patients with biliary disease.

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INTRODUCTION

According to nationwide estimates, approximately 20.5 million Americans between ages 20-74 years have gallstone disease^[1]. Other sources estimate a prevalence in the general population of 10%-15%, however these values may still underestimate the extent of disease. Surgical procedures to address symptomatic cholelithiasis are very common with over 500000 cholecystectomies performed annually^[2]. The spectrum of gallstone disease ranges from simple biliary colic and chronic cholecystitis to severe, life-threatening illnesses such as gangrenous cholecystitis, cholangitis, and biliary sepsis. Despite the many laboratory and radiographic studies available, efficiently identifying patients with a serious underlying biliary infection remains a clinical challenge. Early diagnosis is crucial to prevent rapid clinical deterioration. Selecting reliable and predictive admission variables can facilitate recognizing patients with more severe biliary illness, allowing clinicians to optimize the treatment approach^[3]. One such routinely obtained variable is sodium. Hyponatremia, defined as sodium less than 135 mEq/L, has previously been recognized in the context of a variety of inflammatory and infectious disease states. The pathophysiologic mechanism is likely multifactorial and may be related to the effects of inflammatory cytokines^[4,5]. Hyponatremia has similarly been described in association with intra-abdominal infectious processes, including appendicitis, diverticulitis, and gangrenous cholecystitis^[6-8]. Importantly, no previous study has described hyponatremia over the spectrum of biliary disease. We hypothesized that markers of more severe biliary illness were associated with a predictable decrease in sodium level.

MATERIALS AND METHODS

Using a prospectively collected, comprehensive quality outcomes database containing detailed patient demographics, clinical information, and outcomes spanning from March 1989 to October 2019, we studied 920 patients with gallstone disease (892 at San Francisco VA Hospital, 28 at UCSF Medical Center). Patients were identified by general surgery consultation. The lowest sodium level during the initial acute phase of illness, prior to therapeutic intervention (surgery, endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, percutaneous cholecystostomy tube drainage) was recorded. These values were, in most cases, within 24-48 h of acute presentation or preoperative values. Coincident glucose values were also recorded. Operative report, pathology reports, and radiology imaging studies, were reviewed for the presence of gangrenous cholecystitis, abscess,

perforation, and/or necrotizing pancreatitis.

Illness severity, based on pre-intervention findings, was classified into four groups: (1) None: No clinical infection or inflammatory manifestations; (2) Systemic inflammatory response syndrome (SIRS): One or more of temperature $\geq 100^{\circ}\text{F}$; white blood cell $> 10 \text{ K}/\text{cm}^3$, respiratory rate > 20 breaths/minute, or heart rate > 90 beats/minute; (3) Severe illness: Gallbladder empyema, gangrenous cholecystitis, necrotizing pancreatitis, abdominal or hepatic abscess formation, and/or cholangitis; and (4) Sepsis/multiple organ dysfunction syndrome (MODS): Bacteremia, hypotension, or organ dysfunction/failure. Patients were placed into the most severe group for which they met criteria.

The level of bacterial infection was determined using culture results from gallstones, bile, and blood. Patients were stratified by the highest level of bacterial infection detected. When bacteria were present at multiple levels, the highest bacterial level detected was ascribed. For example, patients with positive gallstone and bile cultures were stratified in the bactibilia group, while cases with positive bile and blood cultures were stratified in the bacteremia group.

The Charlson Comorbidity Index (CCI) was calculated for each patient to assess underlying medical morbidity. The CCI, developed in 1987, assigns a score based on the presence and severity of 19 underlying comorbid conditions^[9]. Using this index, an estimated 10-year survival can be calculated. CCI was analysed as a continuous variable and also in three groups, CCI 0-2, 3-4, and ≥ 5 .

The primary measures assessed were sodium level correlation with illness severity and the presence/location of biliary bacteria. Hyponatremia is defined as serum sodium less than 135.0 mEq/L. Secondary measures determined whether other clinical factors correlated, including: The presence of gangrene (gangrenous cholecystitis, abscess, perforation, or necrotizing pancreatitis), CCI score, age, gender, and/or glucose level.

Statistical analysis

Statistical analysis was performed using analysis of variance for interval parametric data, Chi-squared test for variables on a nominal scale (rates and proportions), and Spearman's correlation for bivariate comparisons of ordinal and interval data. A probability of < 0.05 was considered significant. Multivariate analysis was performed using SPSS (IBM, Version 21). The study was approved by UCSF and San Francisco VA IRB.

RESULTS

Of 920 patients with gallstone disease were studied. The population was predominantly male ($n = 806$, 88%) with mean age of 63 (range 17-104 years). Of 267 (29%) patients had preoperative sodium < 135 mEq/L. Most patients underwent a procedure during their admission and some underwent multiple procedures: 847 (92%) underwent laparoscopic or open cholecystectomy, 113 (12%) underwent cholecystostomy tube placement, 204 (22%) had an endoscopic retrograde cholangiopancreatography (or PTC), and 12 (1%) underwent endoscopic ultrasonography. There were no post-operative deaths. Three patients (two who were DNR), treated non-operatively, died following a sudden cardiac event and/or aspiration pneumonia.

Correlation between sodium levels and age, CCI, illness severity, location of biliary bacteria, presence of gangrenous changes, and glucose is shown in [Table 1](#). Included in this table are results of both bivariate and multivariate statistical analyses.

Age and gender

Age was studied both as a continuous variable and in groups. Three age groups were examined: < 50 years ($n = 150$, 16%), 50-69 years ($n = 487$, 53%), and ≥ 70 years ($n = 283$, 31%). Mean preoperative sodium for each group was 138.3 mEq/L, 136.6 mEq/L, 135.8 mEq/L, respectively ($P < 0.0001$, AVOVA). However, on multivariate analysis, age did not independently correlate with hyponatremia ($P = 0.821$).

On bivariate analysis, sodium significantly correlated with gender ($P = 0.0001$, Spearman's rho). Sodium levels were significantly lower in men than in women, 136.4 mEq/L vs 137.9 mEq/L, respectively ($P = 0.0001$, ANOVA). However, on multivariate analysis, gender did not independently correlate with hyponatremia ($P = 0.452$).

Glucose, triglycerides, and cirrhosis

Blood glucose values were available in 899 (98%) cases. On bivariate analysis, hyponatremia was associated with higher mean glucose (160 vs 130 mg/dL, $P = 0.0001$, ANOVA), but glucose was below 200 mg/dL in 82% of cases with

Table 1 Bivariate and multivariate analysis of sodium level and clinical factors

		n (%)	Na (mEq/L)	Bivariate (P value)	Multivariate (P value)
Age ¹	< 50 yr	150 (16)	138.3	0.0001	0.821
	50-69 yr	487 (53)	136.6		
	≥ 70 yr	283 (31)	135.8		
Glucose ¹	Normal (< 115 mg/dL)	392 (44)	137.6	0.0001	0.127
	Elevated (≥ 115 mg/dL)	501 (56)	135.7		
Illness severity	No infectious manifestations	403 (44)	138.7	0.0001	0.0001
	SIRS	196 (21)	136.7		
	Severe	154 (17)	134.7		
	Sepsis/MODS	167 (18)	133.2		
Bacterial location	None/sterile	396 (45)	138.3	0.0001	0.023
	Gallstone only	60 (7)	137.2		
	Bile	338 (38)	135.4		
	Blood	85 (10)	133.1		
Gangrenous changes	None	732 (80)	137.3	0.0001	0.002
	Gangrene	188 (20)	133.8		
Charlson Co-Morbidity index ¹	0-2	518 (57)	137.4	0.0001	0.001
	3-4	261 (29)	136.2		
	5 or more	140 (14)	134.6		

¹Analyzed as a continuous variable. MODS: Multisystem organ dysfunction syndrome; SIRS: Systemic inflammatory response syndrome; Gangrenous changes: Gangrenous cholecystitis, gallbladder perforation, abscess, necrotizing pancreatitis.

hyponatremia. Diabetic patients had lower sodium levels compared to non-diabetics (135 mEq/L *vs* 137 mEq/L, respectively, $P < 0.0001$, AVOVA). On multivariate analysis, glucose did not independently correlate with hyponatremia ($P = 0.127$).

Triglyceride levels were available in 819 cases (89%). Triglyceride levels were not different among cases with and without hyponatremia (148.6 mg/dL *vs* 153 mg/dL, respectively, $P = 0.534$, ANOVA).

Cirrhosis was uncommon in this series, only 64 (7%) patients had cirrhosis. Average sodium levels were lower in cases with cirrhosis (136.7 mEq/L *vs* 135.9 mEq/L, none *vs* cirrhosis, respectively), but differences were not significant ($P = 0.120$, ANOVA). Contributions from cirrhosis were reflected in the CCI calculation, which was included in the multivariate analysis.

Charlson Comorbidity Index

Comorbidity was studied as both a continuous variable and in groups. Patients were stratified into three groups based on CCI: 0-2 ($n = 518$, 57%), 3-4 ($n = 261$, 29%), and ≥ 5 ($n = 140$, 14%). Based on CCI, the estimated 10-year survival for each group was 90%-98%, 53%-77%, and $\leq 21\%$, respectively. The mean sodium for each group was 137.4 mEq/L, 136.2 mEq/L, and 134.6 mEq/L, respectively ($P = 0.0001$, ANOVA). CCI also independently correlated with hyponatremia on multivariate analysis ($P = 0.001$).

Clinical biliary illness

Among the 618 cases with stones confined to the gallbladder, 257 (42%) had biliary colic, 182 (30%) had uncomplicated acute cholecystitis, and 179 (28%) had complicated acute cholecystitis (empyema, gangrenous cholecystitis, gallbladder perforation, and/or abscess formation). Mean sodium among these three groups was 139 mEq/L, 137.3 mEq/L, and 133.9 mEq/L, respectively ($P < 0.0001$, ANOVA).

Among the 302 cases with common bile duct stones, 84 (28%) had uncomplicated choledocholithiasis, 89 (29%) had pancreatitis, and 129 (43%) had cholangitis. Mean sodium among these three groups were 137.7 mEq/L, 136.4 mEq/L, and 134.2 mEq/L, respectively ($P < 0.0001$, ANOVA).

Illness severity

Patients were categorized into one of four groups (None, SIRS, Severe, MODS) based on illness severity prior to intervention (surgery, endoscopic retrograde cholangiopancreatography, cholecystostomy tube, *etc.*). The distribution of illness severity was: None [403 (44%) cases], SIRS [198 (22%) cases], Severe [151 (16%) cases], and sepsis/MODS [168 (18%) cases]. Mean preoperative sodium for each group was

138.7 mEq/L, 136.7 mEq/L, 134.7 mEq/L, and 133.2 mEq/L, respectively ($P < 0.0001$, ANOVA). On multivariate analysis, illness severity independently correlated with hyponatremia ($P = 0.0001$).

Bacterial culture

Cultures were obtained from gallstones and bile, as well as blood when clinically appropriate. Bacterial cultures were available in 879 cases, while blood cultures were obtained in 359 cases. One or more bacterial cultures were positive in 483 (55%) cases. The presence of biliary bacterial correlated with hyponatremia (135.2 mEq/L *vs* 138.3 mEq/L, biliary bacteria *vs* sterile, $P < 0.0001$, ANOVA) (Figure 1).

In many cases, cultures from multiple sites demonstrated bacterial growth, so cases were stratified by the highest level of bacterial infection detected. 396 (43%) cases had sterile cultures, gallstone culture (alone) was positive in 60 (7%) cases, and bacteremia was detected in 338 (40%) cases. Among 359 cases where blood cultures were obtained, bacteremia was present in 85 (24%) cases. Mean sodium levels from each group were 138.3 mEq/L, 137.2 mEq/L, 135.4 mEq/L, and 133.1 mEq/L, (sterile, gallstone bacteria, bacteremia, and bacteremia, respectively, $P = 0.0001$, ANOVA). On multivariate analysis, ascending level of biliary bacterial correlated with hyponatremia ($P = 0.023$); sodium significantly decreased as bacteria ascended from gallstone colonization to bacteremia. The simple presence of biliary bacteria demonstrated a trend ($P = 0.058$) with hyponatremia.

Presence of gangrenous changes

Patients were included in this group based on the presence of the following: Gangrenous cholecystitis (intraoperative or pathologic diagnosis), gallbladder perforation, pericholecystic abscess, and/or necrotizing pancreatitis. Of the 189 (20.5%) patients with gangrenous changes, 61% had preoperative hyponatremia. Gangrenous changes were associated with significantly lower mean sodium (133.8 mEq/L *vs* 137.3 mEq/L, $P = 0.0001$, ANOVA). On multivariate analyses, gangrenous changes independently correlated with hyponatremia ($P = 0.002$).

Additive effects of clinical factors

Clinical factors that were independently associated with sodium level on multivariate analyses included: Co-morbidity (CCI), illness severity, ascending location of biliary bacteria, and the presence of gangrenous changes. The effects of these factors on sodium level seemed to be additive. As shown in Figure 2, for each level of illness severity, mean sodium is even lower as CCI increased. In addition, as shown in Figure 3, mean sodium was lower for patients with a higher level of biliary bacteria and even lower for those patients who also demonstrated gangrenous changes. Note that even among cases with a sterile biliary tree, gangrenous changes (*e.g.*, necrotizing pancreatitis) correlated with decreased sodium level.

DISCUSSION

This study is the first of such size to describe the relationship between hyponatremia and complex biliary disease. Specifically, it illustrates a progressive decrease in sodium level with worsening disease severity. Patients presenting with more severe infections and illness severity demonstrated a significantly reduced serum sodium. In addition, availability of bacterial culture data allowed us to identify associations between the presence of bacteria and hyponatremia, as well as the influence of ascending levels of bacterial infection (gallstone, bile, or blood) on the degree of sodium reduction. This association could be used clinically at the time of presentation to identify patients at greatest risk of decompensation and to guide treatment^[3].

The importance of hyponatremia as a marker of disease severity has been documented in other studies^[10-22]. Hyponatremia has been reported in the context of medical illnesses and inflammatory disease including congestive heart failure, chronic kidney disease, pneumonia, acute respiratory distress syndrome, meningitis, encephalitis, tuberculosis, human immunodeficiency virus infection, and pediatric malignancies and inflammatory illnesses. These reported associations between medical illness with decreased sodium level are consistent with the results of this study - that of decreasing sodium with increasing CCI. But this numerical straightforward association between CCI and sodium level has not previously been reported.

The importance of acute hyponatremia in surgical outcomes has also been recently reported, with some surgical studies reporting a significantly increased mortality risk with hyponatremia^[4-8,10,23-27]. Sakr *et al*^[23] studied nearly 11000 surgical intensive care unit patients, and demonstrated that hyponatremia at the time of intensive care unit

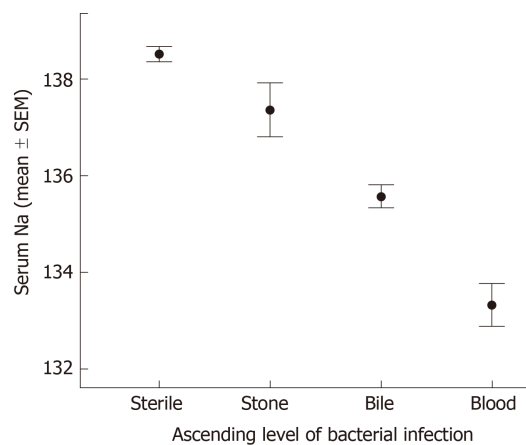


Figure 1 Sodium level - influence of ascending level of biliary bacteria. A higher level of bacterial infection is an independent predictor of lower sodium level, $P < 0.01$.

admission was independently associated with increased risk of in-hospital mortality (16.5% *vs* 7.4%, $P < 0.001$). Using multivariate analysis, Mc Causland *et al*^[24] examined patients undergoing orthopedic surgery and demonstrated an increase in the risk of 30-d perioperative mortality rate associated with decreasing sodium. Leung *et al*^[10] using the ACS NSQIP database, compared 75423 patients with preoperative hyponatremia to 888,840 patients with normal baseline sodium, and noted a higher risk of 30-d mortality (5.2% *vs* 1.3%) in cases with hyponatremia. These findings are consistent with our results and demonstrate the clinical utility of utilizing sodium preoperatively. The results of these studies reflect both the contribution from underlying morbidity and acute illness to surgical outcomes. Our study is unique in that it identified that both of these parameters (co-morbidity and illness severity) are reflected in the sodium level. Further, our study revealed that the sodium level seems to reflect additive contributions from both of these factors. This is an important distinction when analysing the significance of a decreased sodium level.

There is an increasing body of literature to explain potential associations between sodium level and inflammatory/infectious states. Currently, lipopolysaccharide and the inflammatory cytokines TNF- α , IL-1, and IL-6, which are elevated in inflammatory states, are believed to play a key role^[5,28-33]. Studies have demonstrated that increased levels, or intravenous injection, of IL-6 leads to increased release of vasopressin from the hypothalamus^[28]. The antidiuretic effect of vasopressin acting on renal tubule V2 receptors could explain the subsequent hyponatremia. A possible limitation of this theory is a lack of clarity regarding the passage of IL-6 through the blood-brain barrier, but mechanisms have been described^[29]. Multiple studies have also documented the powerful effect of TNF- α on sodium channels, which may explain its role in developing hyponatremia^[30-33]. Schmidt, studying mechanisms of lipopolysaccharide-induced renal dysfunction, demonstrated that injection of TNF- α or IL-1 β increased the production of renal cytokines, decreased expression of renal sodium transporters, and decreased renal function overall^[30]. In other studies, TNF- α has also been shown to interact with amiloride-sensitive, sodium ion channels on the surface of vertebrate cells via N,N'-diacetylchitobiose lectin-like activity, inducing an increase of membrane conductance, causing membrane depolarization^[31-33]. Taken together, these studies explore potential mechanisms for hyponatremia in association with significant inflammatory responses and acute illness caused by complex biliary disease.

Our group has previously shown an association between TNF- α and severe biliary infections. We have had a long interest in the contribution of biliary bacteria to the severity of illness in patients with gallstone disease^[34-43]. We previously identified several bacterial factors that facilitate biliary infection and influence the severity of disease. One such observation was that bacteria present in the biliary tree of patients with more severe biliary illness, produced greater levels of TNF- α in *in vitro* and *in vivo* models^[41-43]. The most virulent bacterial species (from patients with sepsis) were associated with increased TNF- α production. We also noted that elderly patients harbored bacteria with a heightened ability to produce TNF- α , suggesting an important contribution from inflammatory cytokines^[41-43]. This agrees well with the current study given the well-described effect of TNF- α on sodium channels. Reduced sodium level is likely a feature of both acute and chronic inflammatory states, and may reflect an elevated production of inflammatory cytokines. From the observations

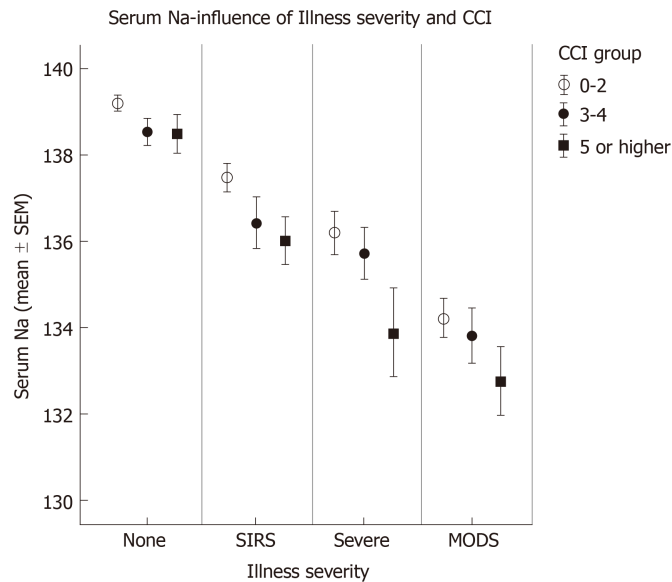


Figure 2 Sodium level - influence of illness severity and Charlson Comorbidity Index score. Illness severity and Charlson Comorbidity Index score (CCI) are both independent predictors of sodium level (Open circles - CCI 0-2; Closed circles - CCI 3-4; Closed squares - CCI 5 or higher). *P* values significant (< 0.01) for all. CCI: Charlson Comorbidity Index.

of this study, these effects are both independent and additive.

We also examined the effect of glucose on sodium levels, to determine if pseudohyponatremia, or dilutional hyponatremia, was a confounding factor. While glucose was significantly increased in patients with preoperative hyponatremia on univariate analysis, the mean glucose was below 200 mg/dL in 80% of cases, indicating there was likely little effect on sodium levels. In addition, glucose did not independently correlate with hyponatremia on multivariate analysis. While glucose remains a useful parameter, it did not appear to be the primary reason for hyponatremia in this study population. Additionally, possible influences from cirrhosis or elevated triglycerides on sodium levels, did not appear to be a factor in this study.

There are some limitations of this study. First, most patients in this study were veterans, a generally older, male-predominant population. While we did note an association between male gender and hyponatremia, male gender did not independently correlate with hyponatremia on multivariate analysis. It remains unclear whether the study population limited our ability to examine contributions made by gender. It is unlikely this would greatly change our findings since women more commonly have cholesterol gallstones, which are generally sterile^[37,40].

On the other hand, men and elderly patients are more likely to harbor biliary bacteria, so our population is ideal for studying the effects of biliary infection on sodium levels. Furthermore, this elderly population is more medically complex, facilitating our investigation into the role of co-morbid disease and hyponatremia. While the study time period was long (reflecting our long-term interest in biliary infections), there was continuity assured by the senior author and methods for managing biliary disease were consistent throughout the period.

In conclusion, this unique, large study is the first to explore, with such granularity, the relationship between complicated biliary disease and sodium levels. No prior studies have examined specific culture and clinical data, as these results are often not readily available in administrative databases. While other studies identified an association between chronic and acute medical illness on sodium levels, this study revealed that both underlying medical morbidity and acute illness severity contribute to decreased sodium levels, and that the effects are additive. This unique observation has not been previously reported. The study illustrates an inverse, independent correlation between illness severity and sodium level. Culture data demonstrate that sodium decreases as bacterial infection ascends from gallstone colonization to bactibilia to bacteremia. Patient comorbidity and the presence of gangrenous changes also independently correlate with sodium on multivariate analysis. Sodium is an important clinical indicator of underlying disease severity for patients with biliary disease.

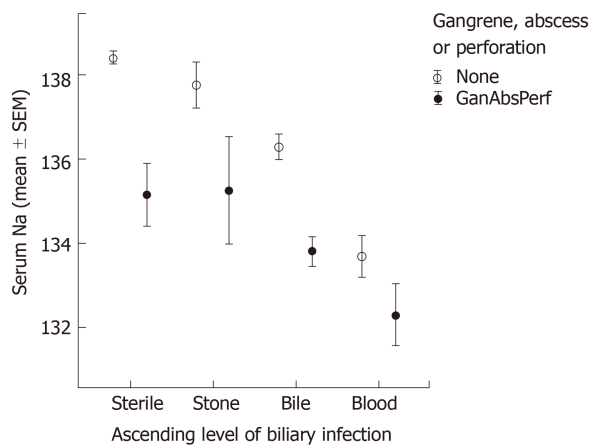


Figure 3 Sodium level - Influence of the level of bacterial infection and presence of gangrene. A higher level of biliary infection and the presence of gangrene are both independent predictors of sodium level (Open circles - absence of gangrene; Closed circles - presence of gangrene). *P* values significant (< 0.01) for all pairings.

ARTICLE HIGHLIGHTS

Research background

While hyponatremia has been studied in the context of other infectious and inflammatory disease states, sodium level has not yet been studied in a large-scale clinical study of patients with severe biliary disease. Serum sodium a common initial laboratory test for patients presenting with biliary disease, may serve as an important diagnostic tool for assessing the underlying severity of illness.

Research motivation

Despite advances in both laboratory and radiographic technologies, identifying patients with severe biliary disease remains a challenge for health care providers in the acute setting. We felt that serum sodium could serve as a critical tool in identifying patients with severe illness, accelerating their care, and improving patient outcomes.

Research objectives

We sought to clarify the relationship between serum sodium and severe biliary disease. Specifically, our goals were to determine if a correlation existed between serum sodium and both illness severity and the presence/location of biliary bacteria. We also sought to determine if such a correlation existed with other clinical factors including the presence of gangrenous changes, Charlson comorbidity score, and glucose level.

Research methods

We utilized a prospectively collected, comprehensive quality outcomes database containing detailed patient demographics, clinical information, and outcomes spanning from March 1989 to October 2019 with 920 patients with gallstone disease. The lowest sodium level during the initial acute phase of illness, prior to therapeutic intervention was recorded. We determined illness severity based on pre-intervention findings and classified patients accordingly. The level of bacterial infection was determined using culture results from gallstones, bile, and blood; patients were stratified by the highest level of bacterial infection detected. Patients were also stratified by the Charlson Comorbidity Index.

Research results

We observed a progressive, statistically significant decrease in sodium level with worsening disease severity. We also observed an incremental decrease in serum sodium with ascending bacterial infection. Charlson Comorbidity Index and the presence of gangrenous changes were also independent predictors of decreased sodium on multivariate analysis.

Research conclusions

This study is the first to describe an inverse relationship between serum sodium and severity of biliary disease. Furthermore, it reveals that both underlying medical morbidity and acute illness severity contribute to decreased sodium levels, and that the effects are additive. This study justifies the use of serum sodium as a clinical predictor of the severity of biliary disease.

Research perspectives

The direction of future research regarding patients with low serum sodium and biliary disease should focus on the pathophysiologic cause of decreased serum sodium. The applications of this research have implications not only for patients with biliary disease, but with any inflammatory or infectious process.

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