Practical Laboratory Medicine 19 (2020) e00155

Contents lists available at ScienceDirect

Practical Laboratory Medicine

journal homepage: www.elsevier.com/locate/plabm

Review of interference indices in body fluid specimens submitted for clinical chemistry analyses

Renee L. Eigsti, Matthew D. Krasowski, Aditi Vidholia, Anna E. Merrill *

Department of Pathology, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA, 52242, USA

ARTICLE INFO

Keywords:
Body fluid analysis
Clinical chemistry
Interference
Hemolysis
Icterus
Lipemia

ABSTRACT

Objectives: The aims of this study were to retrospectively investigate interference indices in a wide range of body fluid specimens and compare these indices to those found in serum/plasma.
Design and Methods: This retrospective study evaluated interference indices for hemolysis, icterus, and lipemia in 2752 body fluid specimens submitted for clinical chemistry testing.
Results: The distribution of interference indices for body fluid samples was generally similar to that of serum/plasma interference indices. Hemolysis of specimens submitted for lactate dehydrogenase (LD) represented the most common interference for body fluid chemistries. Body fluids collected from postsurgical drain sites had a higher proportion of tests exceeding both icterus and lipemic limits compared to serum/plasma specimens.
Conclusions: Overall, degrees of hemolysis, icterus, and lipemia observed in body fluid specimens were in large part similar to serum/plasma specimens, with a few notable differences. Body fluids exhibited a higher proportion of samples with severe icterus or lipemia. Severely lipemic body fluid samples were significantly less likely to also be hemolyzed relative to severely lipemic serum/plasma specimens. LD was the test most commonly affected by interference across all body fluid types. False elevations in pleural fluid LD induced by hemolysis can lead to mis-classification of transudative effusions as exudative using Light's criteria. The possible impact of interferences on clinical chemistry testing in body fluids is an important post-analytical consideration.

1. Introduction

Analytical testing on body fluid specimens is a challenging aspect of clinical chemistry [1–4]. Body fluids, defined as specimens other than plasma, serum, or urine, include cerebrospinal fluid (CSF), dialysate, postsurgical drain fluid, wound fluid, and other fluids often obtained using ultrasound-guided aspiration (such as pancreatic, pericardial, and pleural fluid). Analysis of body fluids is clinically relevant in specific situations. For example, Light's criteria compare pleural fluid total protein (TP) and lactate dehydrogenase (LD) with serum measurements to differentiate between exudate and transudate effusions, resulting in different therapeutic strategies [5,6]. Calculation of the serum ascites albumin gradient (SAAG) relies on the measurement of albumin in peritoneal effusions and serum to determine whether the ascites is a result of portal hypertension [7]. Other clinically relevant tests on body fluids include measuring cholesterol and triglycerides in pleural fluid to detect chylothorax and pseudochylothorax, glucose for infectious or malignant effusions,

* Corresponding author. University of Iowa Hospitals and Clinics, Department of Pathology, 200 Hawkins Drive, 6234 RCP, Iowa City, IA, 52242, USA.
E-mail addresses: renee-eigsti@uiowa.edu (R.L. Eigsti), mkrasows@healthcare.uiowa.edu (M.D. Krasowski), aditi-vidholia@uiowa.edu (A. Vidholia), anna-merrill@uiowa.edu (A.E. Merrill).

https://doi.org/10.1016/j.plabm.2020.e00155
Received 8 April 2019; Received in revised form 4 February 2020; Accepted 5 February 2020

amylase to detect postoperative pancreatic fistulas, creatinine and urea nitrogen to detect urinary leakage, and total bilirubin to detect biliary leaks [8–13].

Analysis of these samples is difficult for many reasons. There can be pre-analytical errors in sample labeling and collection [14]. Analytical variation has been proposed due to possible matrix effects [15]. Post-analytical errors may occur due to the absence of reference ranges, leading to variation in result interpretation. One characteristic of body fluids that makes analysis difficult is the potential presence of high concentrations of lipids, bilirubin, hemolyzed cells, and/or other interfering compounds and the lack of established interference limits [1,3,16]. While body fluid testing has been performed for many years in clinical laboratories, laboratory accreditation agencies including the College of American Pathologists (CAP) have recently changed their requirements for body fluid testing to include validation methods [17]. Consequently, as these sample sources are generally not included as valid specimen types by assay manufacturers, individual laboratories must undertake responsibility for validation.

This study aimed to assess semi-quantitative estimates of hemolysis, icterus, and lipemia in body fluid specimens submitted for chemistry analysis. We utilized retrospective data from the centralized core laboratory at an academic medical center covering nearly 3000 body fluid specimens. To assess the prevalence of these interferences and possible impact on result quality, we benchmarked body fluid indices to indices measured in serum/plasma specimens analyzed in the same clinical laboratory.

2. Materials and methods

The study was conducted at the University of Iowa Hospitals and Clinics (UIHC), an 811-bed tertiary/quaternary care academic medical center, following approval by the University of Iowa Institutional Review Board (IRB ID #201803726). Historical chemistry results from 2/1/2017 to 2/28/2018 of 2752 body fluid specimens and from 2/1/2018 to 2/28/2018 of 25,507 serum/plasma specimens were obtained from Epic (Epic Systems, Inc., Madison, WI, USA), versions 2014 (prior to 8/26/2017) and 2017 (8/26/2017 until present), the current electronic health record (EHR). As described in our previous studies, Reporting Workbench functionality within Epic and Healthcare Enterprise Decision Intelligence (HEDI; an institutional data warehouse) allowed for the collection of past laboratory results [18,19].

Automated clinical chemistry testing was performed on the cobas 8000 analyzers (c502 and c702; Roche Diagnostics, Indianapolis, IN, USA). The following 12 chemistry tests were studied: albumin, alkaline phosphatase (ALP), amylase, total bilirubin, blood urea nitrogen (BUN), cholesterol, creatinine (enzymatic), glucose, LD, lipase, TP, and triglyceride. The hemolysis, icterus, and lipemia indices were determined on all plasma, serum, and body fluid specimens using spectrophotometry, as previously described [20]. Unlike serum/plasma test results, the test results of body fluids are reported to the EHR without a comment even if the interference limits have been exceeded. The serum/plasma interference limits for each studied laboratory test were obtained from the Roche cobas package insert versions in production during the period of retrospective study (Table 1). Middleware software (Instrument Manager, version 8.14) from Data Innovations (Burlington, VA, USA) was used for interfacing in the laboratory and also captured the interference indices for each specimen, which were then merged with the data from the EHR [21,22]. The chi-square test of independence was utilized for statistical analyses (Microsoft Excel).

3. Results

3.1. Body fluid categorization

The body fluids were divided into seven anatomic site categories (abdominal, dialysate, drains, pancreatic, pericardial, pleural, and miscellaneous) based on sample labeling and chart review. The miscellaneous category contained anatomic sites comprising <1% of the total number of samples and included CSF, cyst, gastric, hepatic, respiratory secretions, stool, synovial fluid, thyroid/parathyroid, vaginal, and wound. Table 2 shows the breakdown of laboratory tests ordered by body fluid site. Abdominal fluid was the most common body fluid specimen (34% of all specimens), while TP, albumin, and creatinine were the most common tests ordered (19%, 15%, and 15% of all tests ordered, respectively).

Table 1
Plasma/serum interference indices.

Laboratory test	Hemolysis (H index)	Icterus (I index)	Lipemia (L index)
Albumin	1000	60	550
ALP	500[a]	60	2000
Amylase	500	60	1500
Total Bilirubin	800	None	1000
BUN	1000	60	1000
Cholesterol	700	30[a]	2000
Creatinine	800	60[a]	2000
Glucose	1000	60	1000
LD	50[a]	60	900
Lipase	1000	50	2000
TP	500	40[a]	2000
Triglyceride	700	35	None

[a] denotes index established by the laboratory as opposed to Roche package insert.

Table 2
Body fluid specimens organized by anatomic site with corresponding laboratory tests ordered.

Laboratory test	Abdominal (n = 942)	Dialysate (n = 270)	Drains (n = 933)	Pancreatic (n = 27)	Pericardial (n = 59)	Pleural (n = 466)	Miscellaneous (n = 55)	Total (n = 2752)
Albumin	763	0	1	0	3	38	2	807
ALP	60	0	0	0	1	9	1	71
Amylase	124	2	437	24	2	44	4	637
Total Bilirubin	32	0	80	0	0	8	5	125
BUN	9	262	0	0	1	0	0	272
Cholesterol	2	0	0	0	48	40	4	94
Creatinine	36	264	443	0	2	2	27	774
Glucose	94	40	1	1	50	298	2	486
LD	131	0	1	0	53	366	10	561
Lipase	77	2	82	5	1	8	6	181
TP	569	0	4	0	50	369	11	1003
Triglyceride	83	6	34	1	6	118	8	256

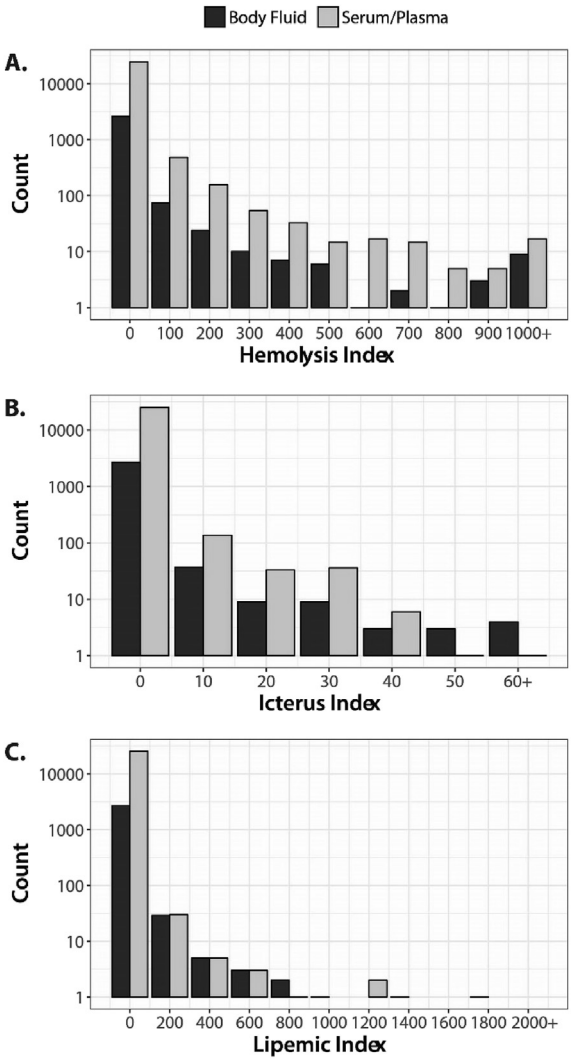


Fig. 1. Distributions of a) hemolysis, b) icterus, and c) lipemic indices in body fluids compared with serum/plasma specimens. The number of specimens is plotted on a logarithmic scale.

3.2. Distribution of interference indices

The distributions of body fluid interference indices compared with serum/plasma are illustrated by absolute count and proportion in Figs. 1 and 2, respectively. These distributions are parsed by anatomic site in Fig. 3. The distribution of the body fluid hemolysis indices was similar to serum/plasma (Fig. 1a), with approximately 95% of all samples displaying a hemolysis index of less than 100 (Fig. 2a). The median hemolysis indices for drain and pericardial specimens (15 and 10, respectively) either equaled or exceeded the median hemolysis index for serum/plasma specimens (10, Fig. 3a). In contrast, body fluid specimens had a higher range of icterus indices, with seven samples at or above 50 (Figs. 1b and 2b); the icterus index did not exceed 45 in any of the serum/plasma samples evaluated. Total bilirubin concentrations were ordered in all seven severely icteric body fluid samples and agreed well with the icterus indices (mean bias 2%, range −13%–42%). Six of the seven samples were collected from postoperative drains following abdominal surgery with a history consistent with a biliary leak due to either trauma or gallbladder perforation. The remaining sample was a respiratory secretion from a patient with concern for a hepato-bronchial fistula. These anatomic sources are expected, as drain and pericardial specimens overall demonstrated higher mean icteric indices (2.3 and 2.6, respectively) relative to serum/plasma specimens (1.3, Fig. 3b). Three of the seven samples with an icteric index 50 or higher had laboratory tests of amylase, creatinine, and lipase that exceeded the respective icteric limits (Table 1). The potentially affected chemistry tests all employ enzymatic reactions with colorimetric detection. In addition, high concentrations of bilirubin are known to cause falsely lowered enzymatic creatinine measurements due to quenching of the hydrogen peroxide intermediate [23]. Consistent with this prior finding, creatinine was low (0.3 mg/dL) in one of the severely icteric drain fluids, which could represent negative interference by excess bilirubin.

Body fluids were also significantly over-represented in specimens with lipemic indices of 500 or higher, $\chi^2 = 36.0$, $p = 1.9 \times 10^{-9}$ (Figs. 1c and 2c). In fact, lipemic indices for two body fluid specimens exceeded 1500. One of the lipemic samples was from a

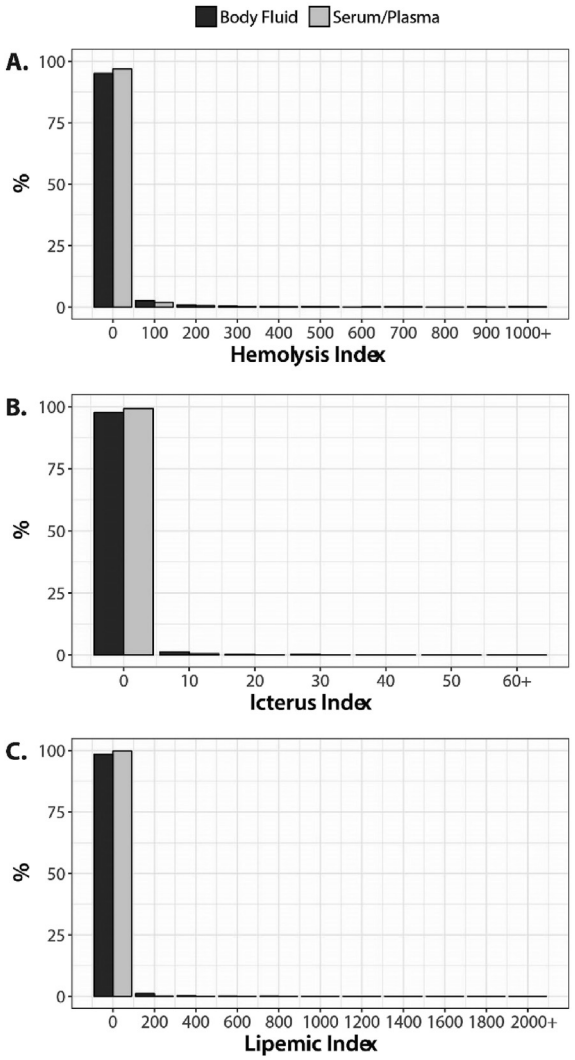


Fig. 2. Percentage distribution of a) hemolysis, b) icterus, and c) lipemic indices in body fluids compared with serum/plasma specimens.

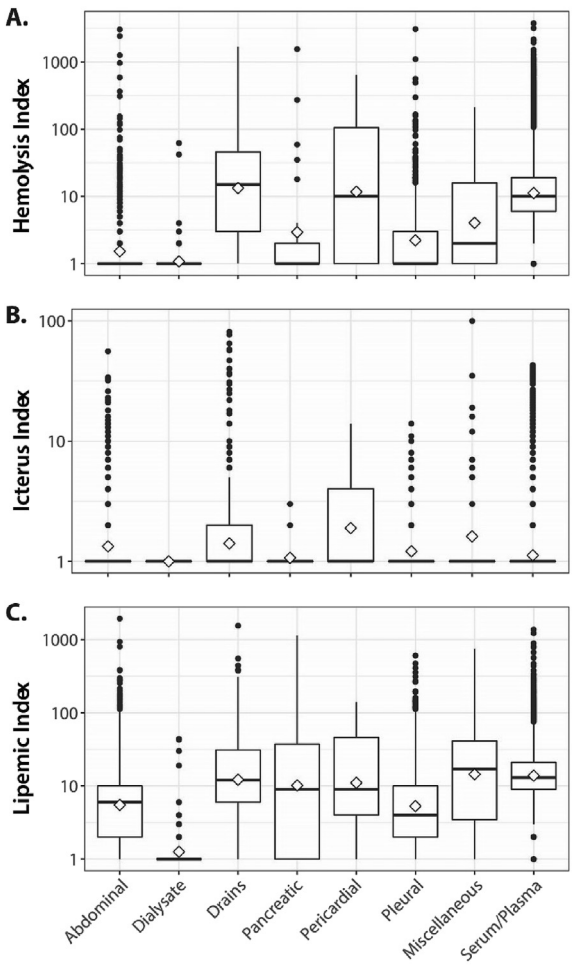


Fig. 3. Box plots illustrate the distributions of a) hemolysis, b) icterus, and c) lipemic indices by anatomic site. The box indicates the inter-quartile range (IQR, 25th-75th percentile of the data), the line indicates the median, the diamond indicates the mean, the whiskers extend to the furthest data point that is within 1.5 times the IQR, and the dots indicate outliers. The indices are plotted on a logarithmic scale.

postoperative neck drain of 55 year-old male status post a neck dissection for malignancy with clinical concern for a chyle leak. The triglyceride concentration in this fluid was 3525 mg/dL and the amylase ordered on this specimen exceeded the established serum/plasma limit for lipemia. The other lipemic sample was ascites from an 8-day-old preterm infant found to have extravasated total parenteral nutrition in the abdomen from a leaking umbilical venous catheter. This sample yielded a triglyceride concentration of 2082 mg/dL and the glucose ordered on this specimen exceeded the established serum/plasma limit for lipemia. The potentially affected assays rely on photometric detection at relatively short wavelengths (415 nm for amylase and 340 nm for glucose), where excess turbidity could obscure accurate measurement. Of note, all non-miscellaneous specimen sources displayed lower median lipemic indices compared to serum/plasma samples.

3.3. Relationship between interference indices

The relationship between different interferences can suggest certain pathologies, such as elevated serum/plasma hemolysis and icterus in hemolytic anemia cases. In both body fluid and serum/plasma samples, increasing hemolysis severity appears correlated with increasing lipemia severity (Fig. 4a). Previous studies have reported an association of severely lipemic specimens with increased hemolysis in serum/plasma samples [20,24]. Some highly lipemic body fluid samples exhibit severe hemolysis, but most are relatively unaffected by hemolysis. For example, when considering body fluid specimens with a lipemic index of 250 or higher (approximately 1% of body fluid samples), 33% demonstrated a hemolysis index of 50 or higher (median 25.5); in contrast, 97% of serum/plasma samples with a lipemic index of 250 or higher had a hemolysis index of 50 or higher (median 495). Therefore, compared to serum/plasma samples, the most severely lipemic body fluid samples are less likely to also be hemolyzed, $\chi^2 = 22.6$, $p = 4.3 \times 10^{-7}$. There does not seem to be a relationship between icterus and hemolysis (Fig. 4b) or icterus and lipemia (Fig. 4c) in either body fluid or serum/plasma specimens.

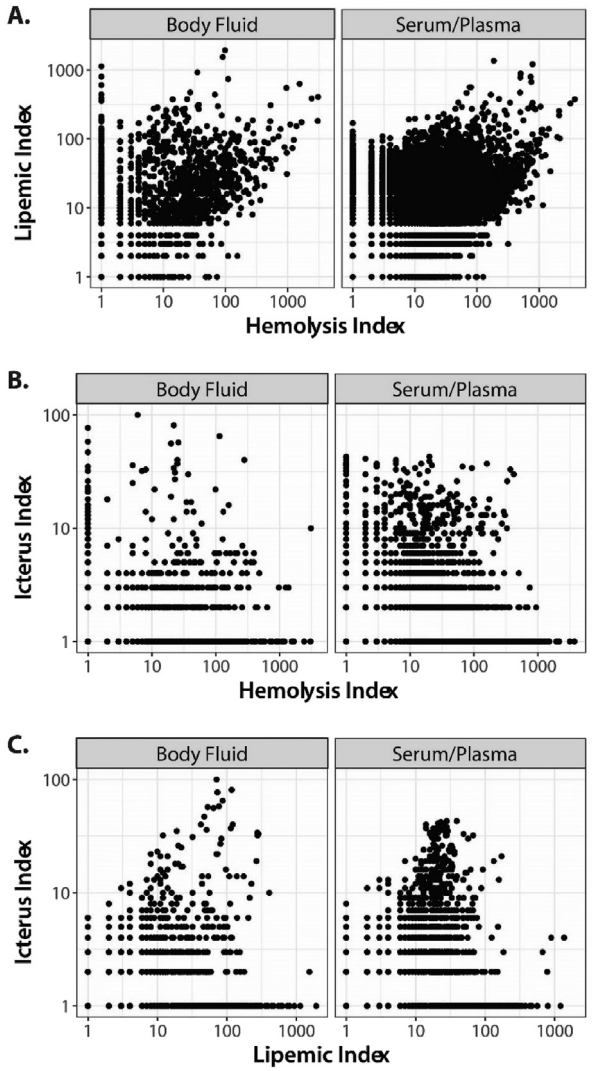


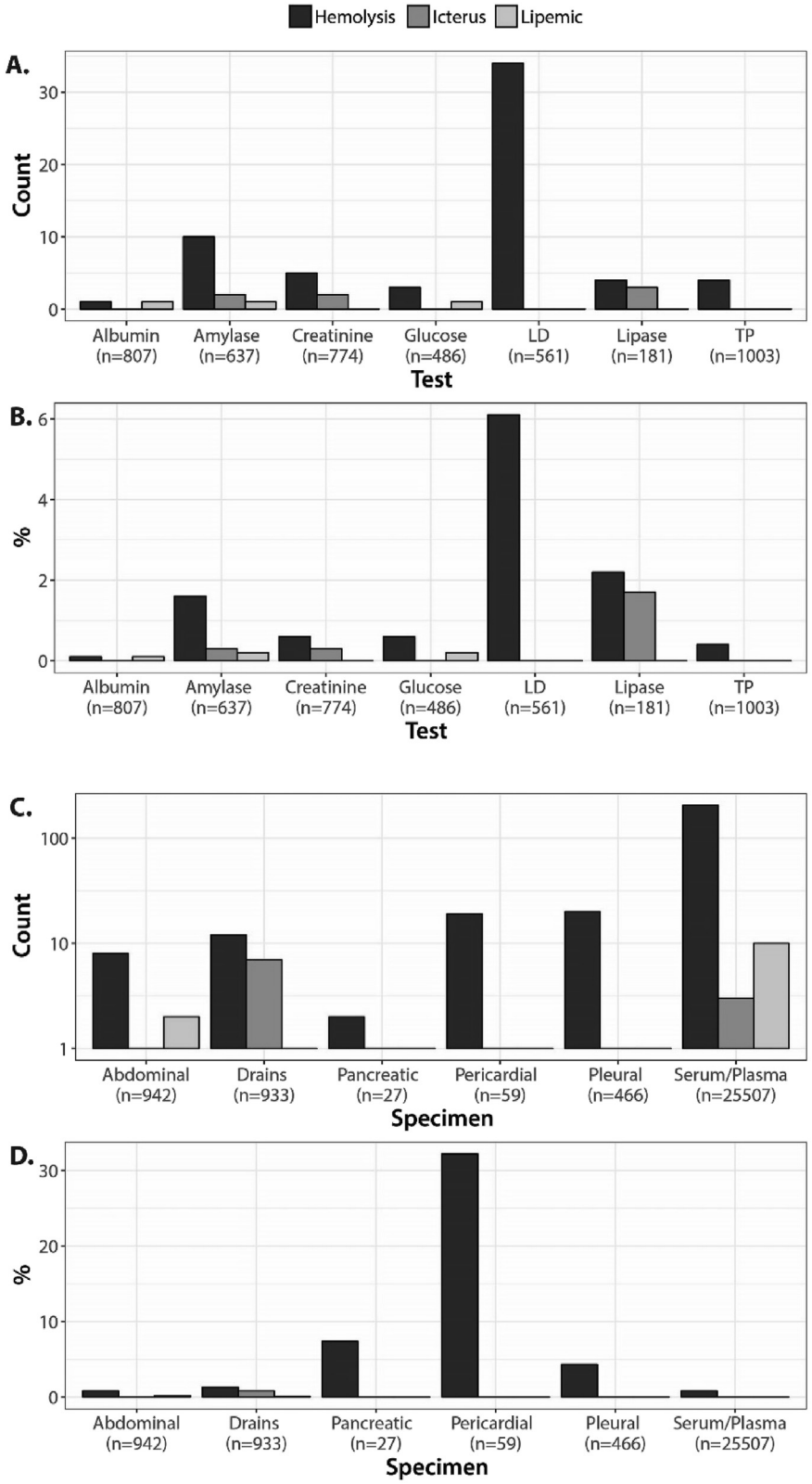
Fig. 4. The relationships between a) lipemia and hemolysis, b) icterus and hemolysis, and c) icterus and lipemia displayed for both body fluid and serum/plasma specimens. All axes are plotted on a logarithmic scale.

3.4. Proportion of body fluid indices exceeding the established corresponding plasma limit

The absolute number and proportion of body fluid indices above the established corresponding serum/plasma limit were plotted by laboratory test (Fig. 5a and b). The absolute number and proportion of samples with indices above the limit for at least one ordered test were plotted by anatomic site (Fig. 5c and d). In body fluid specimens, the hemolysis limit was most commonly exceeded for LD (6.1% of the LD tests ordered on body fluids). This is comparable to serum/plasma samples, where hemolysis in 5.9% of the LD tests ordered exceeded the acceptable limit (data not shown). Other tests from body fluid samples that were affected by hemolysis with similar frequency as serum/plasma samples were albumin, total protein, and triglyceride (<0.5% of tests ordered). Tests on body fluid samples resulting in a higher percentage of potentially significant hemolysis relative to serum/plasma samples were lipase (2.2%), amylase (1.6%), creatinine (0.6%), and glucose (0.6%); fewer than 1 in 1000 (0.1%) of these tests in serum/plasma specimens had hemolysis indices exceeding the limit.

Icterus and lipemia affected far fewer tests across all specimen types when compared to hemolysis. The body fluid tests that most commonly exceeded their respective icterus limit were lipase (1.7%), amylase (0.3%), and creatinine (0.3%); in serum/plasma, icterus affected fewer than 0.1% of these tests. When evaluating tests affected by lipemia, 0.2% or fewer exceeded their respective lipemic limits in both body fluid and serum/plasma specimens.

When evaluating interferences by anatomic site, body fluids from postoperative drains, pancreas, pericardium, and pleura were more affected by hemolysis than serum/plasma samples. Pericardial effusions exhibited the highest rate of samples affected by hemolysis (32.2%); in 18 of 19 specimens where the serum/plasma hemolysis threshold was exceeded, the affected test was LD. This mimics the



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results from pleural fluids, in which LD accounted for 15 of the 20 hemolyzed samples. Body fluids collected from postsurgical drain sites had a higher proportion of tests exceeding both icterus and lipemic limits compared to serum/plasma specimens.

4. Discussion

Body fluids present a challenge for clinical chemistry analysis due to their wide variety of sources and possible matrices [1–4]. An additional complication is that most body fluids are not included as valid specimen types by assay manufacturers. Thus, assay performance characteristics, including interference studies, are generally not available unless found in the published literature or determined by individual laboratories.

This manuscript reviewed the measurement of traditional interference indices (i.e., hemolysis, icterus, and lipemia) in body fluids. Previous studies have found that interference limits for body fluids determined during assay validation generally correlate with the serum/plasma limits, suggesting that matrix effects do not significantly impact the effect of these interferences on analyte measurements [1,3,16]. However, these studies do not evaluate whether the frequency or severity of these interferences differs by anatomic site. Our data show that body fluid specimens exhibit distributions of hemolysis, icterus, and lipemic indices similar to serum/plasma specimens. We did not observe any statistical relationship between any of the spectrophotometrically estimated interferences in body fluid specimens. In general, some highly lipemic body fluid samples also resulted in more severe hemolysis, but this pattern was significantly more evident in serum/plasma samples [20,24]. One of the limitations of our study was the retrospective, observatory nature, in that we did not alter the samples to determine the tolerable degree of interference in individual assays. Another limitation of our study is that it was performed at a single center as opposed to collecting data from multiple centers, which may have resulted in a wider variety of body fluid specimens and results.

Applying to body fluid specimens the standard serum/plasma interference index limits found in the assay manufacturer's package insertsrevealed which anatomical sites were more prone to possible interference. Specimens from postoperative drain, pancreatic, pericardial, and pleural sources more frequently exceeded index limits. This may be due to the type of tests ordered from these particular anatomic regions, such as frequent ordering of LD, a test with a relatively low interference limit for hemolysis. In fact, LD represented less than 1% of all tests ordered in serum/plasma specimens, but approximately 10% of tests ordered in body fluid specimens. Hemolysis can impact clinical evaluation of pleural effusions using Light's criteria, leaving transudates at risk of being mis-classified as exudates based on artificially elevated LD measurements. In our data set, all pleural fluid specimens with a hemolysis index above the limit for LD met the requirements for exudative effusions, while 67% of pleural fluids with acceptable hemolysis for LD were classified as exudates. The complex composition of the source fluid, such as a highly turbid drain fluid, may also affect the measurement of interference indices. In addition, other compounds present in body fluids may mimic hemolysis, icterus, or lipemia by absorbance in the wavelengths used by clinical chemistry analyzers for spectrophotometric determination of interference indices.

There are various ways to report chemistry results on body fluid samples in the context of possible interference. One option is to report out all laboratory values regardless of the interference severity with a comment stating that performance characteristics and reference ranges have not been verified. Another approach is to flag results if they exceed the interference limits, yet still report the potentially affected laboratory values; the interference limits of body fluids may not be the same as serum/plasma interference limits, however, as clinically tolerable error likely varies depending on specimen source. For example, while biases of 10–15% induced by interferences may be clinically significant in serum/plasma creatinine measurements used for monitoring renal function, a systematic error of similar magnitude may not change interpretation of creatinine concentration in a postoperative drain fluid, where it is utilized semi-quantitatively to infer a urine leak. Consequently, this would require validation studies to define analyte- and source-specific interference thresholds. Yet another option involves diluting the specimen to remove the interference, which may be appropriate in some scenarios, but not in others (e.g., LD in a hemolyzed sample). Finally, analyte-specific cancellation of body fluid testing is one possible strategy to mitigate interference, as described by a previous study [1]. Due to the wide variety of applications of body fluid measurements, development of thresholds for flagging or cancelling a test may need to be dependent on the clinical utility of the specific laboratory test in a particular matrix. A major consideration with body fluids is that specimen collection is more invasive compared to serum/plasma and recollection is rarely a viable option.

5. Conclusions

Body fluids present a challenge for clinical laboratories due to complexities in the pre-analytical, analytical, and post-analytical phases of the total testing process. Herein, we evaluated hemolysis, icterus, and lipemic indices in nearly 3000 body fluid specimens, including abdominal, pancreatic, pericardial, pleural, dialysate, and postoperative drain sources. In general, the distribution of interference indices in body fluid samples was similar to serum/plasma samples, though body fluids exhibited a higher proportion of samples with severe icterus or lipemia. Severely lipemic serum/plasma samples were significantly more likely to also be hemolyzed

Fig. 5. Distribution of indices exceeding the corresponding interference limit. The absolute and relative quantity of indices above the established corresponding serum/plasma interference limits are plotted by laboratory test (a and b). The absolute and relative quantity of samples with at least one index above the limit are plotted by anatomic site (c and d). The number of specimens in panel C is plotted on a logarithmic scale. The following tests are not plotted as no body fluid specimens exceeded the corresponding interference limits: ALP, total bilirubin, BUN, cholesterol, and triglyceride. The following body fluid specimen categories are not plotted as none of the ordered testing exceeded the corresponding interference limits: dialysate and miscellaneous.

relative to severely lipemic body fluid specimens. LD was the test most commonly affected by interference across all specimen types, while pericardial, pancreatic and drain fluids were the most commonly affected anatomic sites. In particular, false elevations in pleural fluid LD induced by hemolysis can lead to mis-classification of transudates as exudates using Light's criteria. The possible impact of hemolytic, icteric, and lipemic interferences on clinical chemistry testing in body fluids is an important post-analytical consideration.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None of the authors have any conflict to report.

CRediT authorship contribution statement

Renee L. Eigsti: Investigation, Formal analysis, Visualization, Writing - original draft. **Matthew D. Krasowski:** Conceptualization, Writing - review & editing. **Aditi Vidholia:** Data curation, Writing - review & editing. **Anna E. Merrill:** Conceptualization, Investigation, Formal analysis, Visualization, Writing - original draft.

Acknowledgements

None.

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