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Blunt splenic injury: Assessment of follow-up CT utility using quantitative volumetry

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Purpose: Trials of non-operative management (NOM) have become the standard of care for blunt splenic injury (BSI) in hemodynamically stable patients. However, there is a lack of consensus regarding the utility of follow-up CT exams and relevant CT features. The purpose of this study is to determine imaging predictors of splenectomy on follow-up CT using quantitative volumetric measurements.

Methods: Adult patients who underwent a trial of non-operative management (NOM) with follow-up CT performed for BSI between 2017 and 2019 were included (n = 51). Six patients (12% of cohort) underwent splenectomy; 45 underwent successful splenic salvage. Voxelwise measurements of splenic laceration, hemoperitoneum, and subcapsular hematoma were derived from portal venous phase images of admission and follow-up scans using 3D slicer. Presence/absence of pseudoaneurysm on admission and follow-up CT was assessed using arterial phase images. Multivariable logistic regression was used to determine independent predictors of decision to perform splenectomy.

Results: Factors significantly associated with splenectomy in bivariate analysis incorporated in multivariate logistic regression included final hemoperitoneum volume (p = 0.003), final subcapsular hematoma volume (p = 0.001), change in subcapsular hematoma volume between scans (p = 0.09) and new/persistent pseudoaneurysm (p = 0.003). Independent predictors of splenectomy in the logistic regression were final hemoperitoneum volume (unit OR = 1.43 for each 100 mL change; 95% CI: 0.99–2.06) and new/persistent pseudoaneurysm (OR = 160.3; 95% CI: 0.91–28315.3). The AUC of the model incorporating both variables was significantly higher than AAST grading (0.91 vs. 0.59, p = 0.025). Mean combined effective dose for admission and follow up CT scans was 37.4 mSv.

Conclusion: Follow-up CT provides clinically valuable information regarding the decision to perform splenectomy in BSI patients managed non-operatively. Hemoperitoneum volume and new or persistent pseudoaneurysm at follow-up are independent predictors of splenectomy.

KEYWORDS

quantitative CT, volumetry, follow-up, blunt splenic injury (BSI), computed tomography, spleen, trauma, abdominal trauma

Introduction

The spleen is the most commonly injured organ in blunt abdominal injury (1, 2). The spleen is involved in innate and adaptive immunity and response to bacterial infection (3). Splenectomy carries an estimated 5% lifetime risk of overwhelming post-splenectomy infection (OPSI)- a form of fulminant sepsis associated with a mortality between 50 and 80% (4–6). The prevailing treatment strategy for blunt splenic injury (BSI) has moved away from routine operative management to one of selective non-operative management (NOM), involving attempts at salvaging splenic function in hemodynamically stable patients (1, 5, 7). Trials of NOM, with or without adjunct splenic embolization, also allow patients to potentially avoid unnecessary short-term morbidity associated with laparotomy (8). An examination of the American College of Surgeons National Trauma Data Bank found that \sim 85-90% of patients with blunt splenic trauma do not require urgent splenectomy and may be candidates for NOM (9). The failure rate of splenic salvage in patients selected for NOM has a relatively low reported incidence of 8-11% (10-12) and most failures occur within the first 24 h (11).

Failure of non-operative management carries its own increased risk of morbidity and mortality (11, 13) and requires vigilant patient monitoring. There has been variable adoption of follow-up CT in splenic NOM protocols, and this practice remains the subject of debate, with no established consensus at the present time (9, 14-22).

American Association for the Surgery of Trauma (AAST) splenic injury grades correlate with the risk of NOM failure after BSI. In a 2012 systematic review of the literature and metaanalysis of 25 studies Banghu et al. found that AAST grade IV-V injuries and moderate to large hemoperitoneum were significantly associated with increased risk of non-operative management failure (23). In a more recent prospective study of 87 patients in whom AAST grades were assigned based on the patient's admission CT scan, Brillantino et al. found no significant difference in the success rate of NOM based on AAST scoring (24).

While initial management is determined by a combination of the patient's hemodynamic status and admission CT imaging (20), the perceived value of follow-up inpatient CT imaging in patients selected for NOM lies in the ability to track the natural history of splenic injury and directly visualize potential leading indicators of delayed splenic rupture. These include worsening hemoperitoneum, laceration, subcapsular hematoma, and new or non-resolving pseudoaneurysms. The use of follow-up CT alongside vital sign monitoring and serial hemoglobin testing during inpatient NOM trials has been found to have utility in several published studies (14, 17, 18).

Cumulative radiation from repeat scanning remains a concern in BSI patients (25) and must be weighed when

considering whether to adopt an NOM protocol incorporating follow-up CT. Given conflicting findings, ongoing debate, the scarcity of literature on the topic, and radiation concerns, the role of follow-up CT remains controversial. According to a 2019 international survey of practice patterns, follow-up CT is used for BSI patients selected for NOM in 38% of trauma centers (26). More study is needed to clarify the role of follow-up imaging and the individual signs predictive of splenectomy.

Where employed, follow-up CT is typically performed within 24-72h (15, 16, 20, 26). Arterial phase CT images are superior for assessment of the presence or absence of pseudoaneurysm (27, 28), while splenic laceration, and subcapsular hematoma are graded in a coarse categorical fashion per AAST grading criteria on portal venous phase images where peak parenchymal enhancement helps delineate organs from adjacent non-enhanced blood (29). Hemoperitoneum volume assessment is usually performed using a coarse subjective method described by Federle and Jeffrey (30), although recently, voxelwise quantitative CT measurement of hemoperitoneum volume has been shown to be more predictive of outcomes in trauma patients than the Federle method (31). Even though hemoperitoneum and other bleeding features in the abdominopelvic region are typically irregular, and multifocal, volumetric measurements have been shown to have high interobserver agreement and repeatability (31-34). In a previous study on hemoperitoneum segmentation, test-retest reliability of repeat hemoperitoneum measurements was high, with both interclass correlation coefficient and Pearson r values of 0.98 (31). CT volumetry provides granular measurements and has been leveraged to study tumor growth rate as a marker of outcome on repeat CT imaging (35, 36) but this is not wellexplored in the trauma domain.

The purpose of this study is to model features of BSI in NOM patients followed with surveillance CT as predictors of splenectomy. Voxelwise measurements of features scored categorically using AAST and Federle grading are measured using CT volumetry to provide a greater level of granularity. The performance of our model is compared with admission CT-based AAST grading as a benchmark.

Materials and methods

Institutional management approach

At our trauma center, in light of the immunological consequences of a potentially avoidable splenectomy, we take a conservative approach using a standard surveillance policy incorporating follow-up contrast-enhanced CT (CECT). Patients sufficiently stable to undergo an initial admission CECT are graded per AAST criteria. Those with grade 5 AAST injuries including active hemorrhage undergo laparotomy.

Follow-up CT in NOM without angiography

Stable patients with AAST grade 2 injuries and no concurrent visceral injuries necessitating laparotomy are triaged for follow-up CT imaging, which typically occurs between 24 and 48 h.

Follow-up CT in NOM with angiography

Those with AAST grade 3 and 4 injuries undergo routine interrogation with angiography and possible angioembolization prior to follow-up CT. Follow-up CT after angiography is typically performed between 48 and 72 h (37). Patients with pseudoaneurysm associated with minimal parenchymal disruption may be observed on a case-by-case basis. All NOM patients with or without angiography are also followed with serial CBC and abdominal exams.

Splenectomy or splenic salvage after follow-up CT

The decision to perform splenectomy is ultimately based on individual surgeon discretion, however it is informed by varying combinations of worsening on follow-up CT (19), deteriorating hemodynamic status (38), or ongoing need for transfusion (39). Worsening on follow-up CT is considered indicative of splenic rupture or high risk thereof. It is characterized by increasing splenic parenchymal disruption, subcapsular hematoma, or hemoperitoneum as well as new or persistent pseudoaneurysm (14, 17, 18). Our protocol does not involve repeat attempts at angiography after follow-up CT. To avoid the potential catastrophic consequences of a delayed splenic rupture, where the surgent deems there is sufficient injury progression, splenectomy is offered.

Patient selection

This work was part of an institutional review boardapproved and HIPAA-compliant study performed at University of Maryland Medical Center and included a retrospectively analyzed cohort of consecutive adult (age \geq 18) patients identified using our electronic medical record who underwent an inpatient trial of NOM with follow-up arterial and portal venous phase contrast-enhanced CT through the abdomen and pelvis between July 1, 2017, and June 30, 2019, with follow-up of splenic injury as the primary indication. Patients who underwent urgent laparotomy following admission (n = 11), or who had follow-up CT for indications other than splenic trauma (n =9) were excluded. The final study cohort was composed of 51 patients (median age 40; 59% male). Splenectomy served as the primary endpoint (n = 6). 45 patients underwent successful splenic salvage (n = 45). Demographic information and results of clinical and laboratory tests were extracted from the electronic medical record (Table 1) including: patient age; gender; systolic blood pressure (SBP), heart rate (HR), hemoglobin (Hgb), and number of units of packed red blood cells transfused (PRBCs) at the time of follow-up imaging. The shock index was derived from HR and SBP. Other covariates collected included the AAST splenic organ injury scale (OIS) grade on admission CT; whether NOM involved proximal or distal adjunct splenic artery embolization; whether angioembolization led to successful splenic salvage or was followed by splenectomy; and days between initial and follow-up imaging (approximated to the nearest minute using study time stamps).

Image analysis

Dual arterial and portal venous contrast-enhanced abdominopelvic trauma CTs were performed from the dome of the diaphragm to the greater trochanters with one of two trauma bay scanners- either a dual source 128-section CT (SOMATOM Force; Siemens, Erlangen Germany), or a 64-section CT (Brilliance; Philips Healthcare, Andover, Mass.) Additional scan parameters included the use of 100 mL of 350 mg/mL Iohexol (Omnipaque; GE healthcare; Boston, Mass.), bolus tracking in the descending aorta individualized by scanner for arterial phase scan timing, followed by a 60–70 s delay for the portal venous phase. Images were archived at 1.5 mm section thickness.

of Voxelwise measurements splenic laceration. hemoperitoneum, and subcapsular hematoma were derived from portal venous phase (PVP) images of the initial and follow-up scans in 3D Slicer (version 4.10.2) (40) labeled in three planes using the 3D threshold paint tool set to \sim 30–80 HU, following methodology described in Dreizin et al. (31, 41, 42). Labeling was performed by a trained research assistant and all scans were subsequently reviewed and edited by a trauma radiologist attending with 10 years of experience. Following manual segmentation, total volumes of each imaging feature were automatically calculated and recorded in milliliters (mL). Presence or absence of new or persistent pseudoaneurysm on follow-up CT was assessed using arterial images.

Statistical analysis

Stata/SE (version 17; College Station, TX) was used for all statistical analysis. For continuous variables, the Mann-Whitney U test was used to compare non-normally distributed data between the splenectomy and splenic salvage groups while a t-test was used to compare mean values of normally distributed data between the two groups. Fisher's exact test was used to compare proportions between the splenectomy and splenic salvage groups.

Covariate	Total cohort $(n = 51)$	Splenectomy $(n = 6)$	Splenic salvage ($n = 45$)	p
Age (median[IQR])	40 (27–61)	63 (31–67)	40 (27–59)	0.56
Gender (<i>n</i> [%])				
Male	30 (59)	3 (50)	18 (40)	0.68
Female	21 (41)	3 (50)	21(38)	
Follow-up SBP ^a (mean[SD])	133.9 (23.4)	141.0 (22.0)	133.0 (23.6)	0.41
Follow-up HR ^b (median[IQR])	84 (74–101)	83 (77–97)	84 (73-100)	0.73
Follow-up SI (median[IQR])	0.65 (0.52-0.78)	0.65 (0.62-0.67)	0.66 (0.50-0.79)	0.77
AE (<i>n</i> [%])	10 (20)	1 (17)	9 (20)	1
Pseudoaneurysm (n[%])	13 (25)	5 (83)	8 (18)	0.003
Time between CTs ^c (h) (median[IQR])	2.0 (1.3, 2.6)	1.4 (1.0, 2.0)	2.0 (1.4, 2.6)	0.11
Change in Hgb (mean[SD])	-2.2 (1.9)	-1.2 (1.5)	-2.3 (2.0)	0.11
PRBCs transfused (mean[SD])	1.7 (2.8)	3.0 (4.1)	1.5 (2.6)	0.15
AAST grade $(n[\%])^d$				0.63
1	2 (3.9)	0 (0.0)	2 (4.4)	
2	31 (61.0)	3 (50.0)	28 (62.2)	
3	12 (23.5)	2 (33.3)	10 (22.2)	
4	6 (11.8)	1 (16.7)	5 (11.1)	

TABLE 1 Demographic and clinical characteristics.

Two-tailed p < 0.05 indicate statistical significance and are bolded.

SD, Standard Deviation; IQR, Interquartile range; SBP, Systolic blood pressure; HR, Heart rate; SI, shock index; AE, Angioembolization; PRBCs, units packed red blood cells transfused. ^aSystolic blood pressure at time of follow-up CT scan.

^bHeart rate at time of follow-up CT scan.

^cTime between initial CT and follow up CT.

^dThere were no conservatively managed grade V BSIs in our sample.

Multivariable logistic regression was used to construct a model including imaging predictors at a significance level of 10% in bivariate analysis (i.e., p < 0.10). Variables included in the full model included final hemoperitoneum volume; final subcapsular hematoma volume; change in subcapsular hematoma volume per day; and presence or absence of pseudoaneurysm on follow-up CT. A backward model selection procedure was used to identify a final reduced model with all predictors that were statistically significant at a level of 10%.

The Hosmer-Lemeshow goodness-of-fit test with 10 quantiles of estimated probabilities was used to determine whether model-predicted probabilities conformed to the observed data, with a p > 0.05 indicating goodness of fit. Area under the ROC curve (AUC) was calculated for the model and assessed qualitatively as a measure of accuracy using a commonly employed grading scale: 0.5–0.59, fail; 0.6–0.69, poor; 0.7–0.79, fair; 0.8–0.89, good; AUC 0.9–1, excellent (43). The model AUC was compared with the AUC of AAST grading.

Results

Baseline characteristics

NOM with follow-up CT was attempted in 51 patients, with 6 patients (12% of the cohort) ultimately requiring

splenectomy. Baseline demographic and clinical characteristics for the splenectomy and splenic salvage groups are shown in Table 1. A median of 2.0 days transpired between admission and follow-up CT (IQR: 1.3-2.6 days). There was a trend toward less time between CTs in the splenectomy group indicating a greater index of clinical suspicion for delayed splenic rupture (DSR), however this did not reach statistical significance (p =0.11). There were no significant differences in age (p = 0.56), gender (p = 0.68), SBP (0.41), HR (0.73), shock index (p =0.77), and change in Hgb (p = 0.11) between the splenectomy and splenic salvage groups, however this may have been related to more aggressive transfusion in the splenectomy group. A mean of 3.0 units PRBCs were transfused in the splenectomy group vs. 1.5 units in the splenic salvage group (p = 0.15). Three patients (one of whom underwent proximal AE) were offered splenectomy after the second study due to perceived high risk of DSR, and 3 patients progressed to DSR on the follow-up exam.

In total, 10 patients underwent AE, with proximal splenic artery embolization in all 10 patients. One patient in the splenic salvage group had a combined proximal and selective coil embolization. There no significant differences in AAST grade were distributions between the splenectomy and splenic salvage groups (p = 0.63).

Covariate	Total cohort $(n=60)$	Splenectomy $(n = 7)$	Splenic salvage (n = 53)	Þ
Final HPvol (mL) (median[IQR])	15.2 (2.1 to 89.3)	187.4 (96.9 to 550.7)	12.1 (0.9 to 53.4)	0.003
Final LACvol (mL) (median[IQR])	0.5 (0.0 to 4.1)	1.2 (0.2 to 10.1)	0.4 (0.0 to 3.2)	0.49
Final SCHvol (mL) (median[IQR])	0 (0 to 0)	5.0 (0 to 11.7)	0 (0 to 0)	0.001
Δ in HPvol/day (mL/day) (median[IQR])	0 (-8.1 to -8.1)	4.2 (-19.8 to 35.9)	0 (-5.6 to 6.7)	0.98
Δ in LACvol/day (mL/day) (median[IQR])	-0.1 (-0.9 to 0.1)	0 (-0.5 to 1.0)	-0.1 (-1.1 to 0.0)	0.52
Δ in SCHvol/day (mL/day) (median[IQR])	0 (0 to 0)	3.0 (0 to 9.9)	0 (0 to 0)	0.09

Two-tailed p < 0.1 are bolded and met inclusion criterion for model selection.

HPvol, Hemoperitoneum volume; LACvol, Laceration volume; SCHvol, Subcapsular hematoma volume.

Predictors (bivariate analysis)—pseudoaneurysm

In total 13 patients (25%) had pseudoaneurysm and 7 of these patients underwent AE. The proportion of patients with new or persistent pseudoaneurysm on followup CT was significantly higher in patients who required splenectomy after failing a trial of NOM (p = 0.003). Pseudoaneurysm on follow-up CT was present in 83% (5/6) of patients who underwent splenectomy and in 18% (8/45) of patients with successful splenic salvage. One patient failed AE and underwent splenectomy for splenic laceration and massive hemoperitoneum (1,415 mL), despite non-visualization of pseudoaneurysm on the follow-up CT scan.

Predictors (bivariate analysis)—volumetric measurements

Table 2 details the final volumes of hemoperitoneum, laceration, and subcapsular hematoma on follow-up CT as well as the rate of change. Only final hemoperitoneum volume (p = 0.003), final subcapsular hematoma volume (p = 0.001) and change in subcapsular hematoma volume per day (p = 0.09) met significance for inclusion in logistic regression, with higher values in the splenectomy group. Final laceration volume and the rate of change in volume for hemoperitoneum, and laceration did not vary significantly between groups.

Multivariable logistic regression model

Predictor variables that remained in the final model after backward elimination steps included hemoperitoneum volume (OR = 1.43 per 100 mL change) and new/persistent pseudoaneurysm (OR = 160.3). Results of regression are shown in Table 3.

TABLE 3 Multivariable model of the relationship between predictor variables and splenectomy.

Predictor	OR	95% CI	р
Final hemoperitoneum volume per 100 mL ^a	1.43	0.99-2.06	0.055
Pseudoaneurysm Yes vs. No	160.3	0.91-28315.3	0.054

OR, odds ratio.

^aEach 100 mL increase in final hemoperitoneum volume corresponds with a 43% increase in odds of splenectomy.

AUC for the model was in the "excellent" range at 0.91 (95% CI: 0.82–0.99). Hosmer-Lemeshow goodness of fit test produced a *p*-value of 0.98, indicating that the model fits the observed data. The AUC for the model was significantly higher than the AUC for admission AAST grading of 0.59 (95% CI: 0.37–0.82, p = 0.025). Examples of initial and follow-up CT imaging for patients who underwent either splenectomy or successful splenic salvage are provided in Figures 1, 2.

Radiation dose

The mean effective dose was 21.3 millisieverts (mSv) (95% CI: 18.2–24.4) for the first scan, and 16.1 mSv (95% CI: 13.1–19.1) for the follow-up scan. On average, the effective dose was 5.2 mSv less on the follow up than on the initial admission exam, with a combined dose of 37.4 mSv (95% CI: 32.4–42.4).

Discussion

Trials of non-operative management have become the standard of care for BSI in initially hemodynamically stable patients. The decision to operate is based on data that suggests a high risk of delayed splenic rupture, and splenectomy is performed in an effort to reduce the risk of uncontrolled splenic bleeding. Vital signs, hemoglobin levels, abdominal signs and symptoms, and blood transfusion requirements are important



grade IV BSI with several pseudoaneurysms in the inferior pole of the spleen (circle on bottom left admission CT image), and 253 mL of hemoperitoneum. This increased to 1,415 mL on follow-up CT performed 49 h later (green label mask, right image). Pseudoaneurysms were no longer visualized but the laceration had expanded to include the upper pole (arrow on top left follow up image).

factors in operative decision-making in patients initially selected for NOM (22, 44). To date, there is a lack of consensus regarding whether follow-up CT has added utility in determining the need for splenectomy after BSI and if so, which CT features are most predictive (14, 15, 17–19, 21, 45). While these issues remain understudied, up to 38% of trauma centers have adopted routine follow up screening CTs in their NOM protocols for BSI patients as of 2019 (26).

Previous reports examining the role of follow-up CT determined that the presence of pseudoaneurysm (19) and subjective hemoperitoneum grading (18) are important predictors of non-operative failure. Multivariable modeling using voxelwise CT measurements of features typically graded in a subjective categorical fashion have been employed in this work to add a greater degree of granularity and objectivity.

We developed a logistic regression model that predicts non-operative failure in patients initially selected for NOM



and rescanned with CT during their hospital course with an AUC of 0.91. Only final hemoperitoneum volume and new or persistent pseudoaneurysm on follow-up CT were predictive of NOM failure and splenectomy in multivariable analysis. Pseudoaneurysm predicted splenectomy with an odds ratio of 160.3. Hemoperitoneum volume unit odds of 1.43 corresponds with a 43% increase in the odds of splenectomy for each 100 mL increase in hemoperitoneum.

Clinical variables were not significantly different between the splenectomy and splenic salvage groups and were not included in multivariable analysis. For example, shock index at the time of follow-up was not significantly different between our splenectomy and splenic salvage samples (p = 0.77), with a median value < 1 (0.65 IQR: 0.62–0.67). The time between initial and follow-up CT trended lower (p = 0.11), and the transfusion requirement trended higher (p = 0.15), pointing to a higher degree of clinical severity in the splenectomy group.

The 12% incidence of splenectomy in our NOM cohort is comparable to the 8–11% incidence described in several prior works (10–12). Grade V injuries are typically managed with urgent splenectomy at our institution, and there were no such injuries in our follow-up CT cohort. We find that once hemodynamically stable patients are selected for an initial trial of NOM using admission CT-based AAST grading, that the resulting narrow distribution of grade II-IV injuries has limited clinical utility for predicting splenectomy. Our model incorporating hemoperitoneum volumes and presence of pseudoaneurysm on follow-up CT had significantly higher AUC than AAST grades for this outcome (0.91 vs. 0.59, p = 0.025).

Radiation concerns remain an important consideration in weighing the risks and benefits of follow-up CT imaging for young BSI patients selected for NOM (25). Evidence from Japanese atomic bomb survivors indicates that doses of ionizing radiation >100 mSv can increase the risk of cancer (46, 47) and this becomes relevant when multiple multi-phase CT examinations are performed over a short period (48). In our sample, the mean combined effective dose was 37.4 mSv (95% CI: 32.4–42.4). No patient received more than 100 mSv of radiation and the minimum age at exam was 24 years.

The immunological consequences of splenectomy should also be considered when implementing an NOM protocol that incorporates follow-up CT. In our splenectomy sample, 3 patients had findings consistent with delayed splenic rupture on follow-up CT, and in the other three, splenectomy was offered following CT due in part to a worsening constellation of imaging findings suggesting impending rupture. The potential benefit of reducing morbidity and mortality using follow-up CT should be weighed against the risk of future OPSI.

Overall, our findings support a role for follow-up CT in patients selected for a trial of non-operative management for BSI. The combination of pseudoaneurysm and hemoperitoneum volume on the follow-up CT study predicted splenectomy with high accuracy.

Our study had several limitations. Even though model AUC was high, our small sample size contributed to wide confidence intervals for the odds ratios of individual predictors. Clinical variables play a critical role in decision-making and lack of significant differences in clinical covariates were also likely related to the sample size. Our CT volumetry-based method provides a more objective and granular quantitative assessment of risk, however quantitative imaging is not currently feasible for BSI patients at the point of care, and this remains a research tool. Mean segmentation times for hemoperitoneum alone exceed 20 min (31). Semi-automated region-growing based algorithms with regulatory approval can potentially be used to obtain measurements of individual features of organ injury or hemorrhage (32, 33, 49), however the effort and expertise required precludes widespread acceptance, especially when multiple features are to be measured (50). Several proofof-concept deep learning-based computer vision algorithms have been reported for rapid quantification of hemoperitoneum and splenic injury burden (31, 51). Steps required before such computer vision technology is ready for clinical adoption include translation into containerized software tools, validation

in simulated deployment studies, regulatory approval, and clinical validation through multi-center studies.

Conclusion

Follow-up CT assists in the decision to pursue splenectomy in BSI patients selected for an initial trial of NOM by providing imaging information that supplements the patient's clinical status. New or persistent pseudoaneurysm and large hemoperitoneum volumes at follow-up are independent predictors of splenectomy. Each 100 mL increase in hemoperitoneum increases the odds of splenectomy by 43%.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by University of Maryland Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

DD, TY, KM, JM, GL, and YL: study concepts/study design or data acquisition or data analysis/interpretation, manuscript revision for important intellectual content, and manuscript final version approval. TY: statistical analysis. TY and DD: original draft preparation and literature research. TY, JM, and DD: manuscript review and editing. DD: funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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