Renal Function–Adjusted D-Dimer Levels in Critically Ill Patients With Suspected Thromboembolism

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Objectives: Diagnosing thromboembolic disease typically includes D-dimer testing and use of clinical scores in patients with low to intermediate pretest probability. However, renal dysfunction is often observed in patients with thromboembolic disease and was previously shown to be associated with increased D-dimer levels. We seek to validate previously suggested estimated glomerular filtration rate–adjusted D-dimer cutoff levels. Furthermore, we strive to explore whether the type of renal dysfunction affects estimated glomerular filtration rate–adjusted D-dimer test characteristics.

Design: Single-center retrospective data analysis from electronic healthcare records of all emergency department patients admitted for suspected thromboembolic disease.

Setting: Tertiary care academic hospital.

Subjects: Exclusion criteria were as follows: age less than 16 years old, patients with active bleeding, and/or incomplete records.

Interventions: Test characteristics of previously suggested that estimated glomerular filtration rate–adjusted D-dimer cutoff levels (> 333 µg/L [estimated glomerular filtration rate, > 60 mL/min/1.73 m^2], > 1,306 µg/L [30–60 mL/min/1.73 m^2], and > 1,663 µg/L [< 30 mL/min/1.73 m^2]) were validated and compared with the conventional D-dimer cutoff level of 500 µg/L.

Main Results: A total of 14,477 patients were included in the final analysis, with 467 patients (3.5%) diagnosed with thromboembolic disease. Renal dysfunction was observed in 1,364 (9.4%) of the total population. When adjusted D-dimer levels were applied, test characteristics remained stable: negative predictive value (> 99%), sensitivity (91.2% vs 93.4%), and specificity (42.7% vs 50.7%) when compared with the conventional D-dimer cutoff level to rule out thromboembolic disease (< 500 µg/L). Comparable characteristics were also observed when adjusted D-dimer cutoff levels were applied in patients with acute kidney injury (negative predictive value, 98.8%; sensitivity, 95.8%; specificity, 39.2%) and/or "acute on chronic" renal dysfunction (negative predictive value, 98.0%; sensitivity, 92.9%; specificity, 48.5%).

Conclusions: D-Dimer cutoff levels adjusted for renal dysfunction appear feasible and safe assessing thromboembolic disease in critically ill patients. Furthermore, adjusted D-dimer cutoff levels seem reliable in patients with acute kidney injury and "acute on chronic" renal dysfunction. In patients with estimated glomerular filtration rate less than 60 mL/min/1.73 m^2, the false-positive rate can be reduced when estimated glomerular filtration rate–adjusted D-dimer cutoff levels are applied. (*Crit Care Med* 2019; XX:00–00)

Key Words: deep vein thrombosis; pulmonary embolism; renal dysfunction; renal failure; renal insufficiency; thromboembolic disease

Thromboembolic disease (TED) often presents with unspecific symptoms (1) and has a high prevalence and mortality (2, 3). Hence, careful diagnostic workup of TED is considered paramount (1). Despite ongoing efforts to improve the diagnosis of TED, clinical outcomes remained rather unchanged during the past decades. Furthermore, hospitalizations due to pulmonary embolism (PE) are rising in the United States (1, 2). In patients with low or intermediate pretest probability, diagnosis of TED is still based on a combination of clinical scores such as Wells score, revised Geneva Score, or Pulmonary Embolism Rule out Criteria score, as well as laboratory workup based on a D-dimer assay (1–3). However, although the sensitivity of D-dimer testing is considered good (99%), its specificity remains reduced (about 40–60%)

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(2, 4). In daily clinical practice, this results in a considerable number of patients in which TED cannot be excluded based on routine clinical and laboratory workup (3). Thus, duplex sonography of the extremities and/or contrast-based chest CT is applied (1, 2). However, respective investigations are costly and involve both radiation and contrast media exposure which may have detrimental side effects (1, 3). Hence, it seems of paramount importance to optimize respective existing diagnostic tools.

D-Dimers are proteins that indicate fibrinolysis and reflect an activated state of coagulation (3, 5). Problematically, however, increased levels of D-dimer proteins are considered highly unspecific. For example, several confounding factors such as age, pregnancy, infections, or liver failure may influence serum D-dimer values (1–3). One additional important confounding factor with a high prevalence in critical illness is renal dysfunction, as elimination of D-dimer protein partly occurs via the kidneys and renal dysfunction is typically associated with a state of chronic hypercoagulation (6). Previous studies suggest that there is a strong correlation between the degree of renal dysfunction and D-dimer levels (7, 8). Our group recently explored the use of renal function–adjusted D-dimer cutoff levels in the critically ill patients (8). The aim of the current investigation was to validate these findings in a large cohort of critically ill patients admitted to a tertiary care academic hospital. Furthermore, we seek to investigate characteristics of estimated glomerular filtration rate (eGFR)-adjusted D-dimer cutoff levels in patients with acute kidney injury and/or "acute on chronic" renal dysfunction.

METHODS

Study Site

The Bern University Hospital, Bern, Switzerland (Inselspital), is one of the largest hospitals in Switzerland with its emergency department (ED) treating more than 45,000 patients per year.

Study Design and Eligibility Criteria

This is a retrospective data analysis using anonymized data from electronic patient charts. Adult patients (defined as > 16 yr) admitted to our ED with a D-dimer and serum creatinine assessment during the 4-year study period (January 2014 to December 2017) were included. The following exclusion criteria applied: patients with active bleeding, D-dimer assessment greater than 24 hours after ED admission, patients with insufficient documentation of *International Classification of Diseases*, 10th Edition (ICD-10) codes and laboratory values (potential reasons include diagnosis not coded by ICD-10 code), missing D-dimer value, and/or missing serum creatinine level. A study flowchart is shown in **Figure 1**.

Data Collection and Extraction

Patients were identified through a combined search for D-dimer and creatinine testing and emergency admission in the hospital database, to identify ED patients admitted for suspected TED. The workup of patients at risk for TED adhered to current clinical guidelines that suggest a combination of clinical evaluation and D-dimer assessment, complemented by radiologic workup, if indicated (3). Respective medical records, laboratory findings, diagnoses, and administrative data were extracted. The following variables were coded: age, sex, race, time between admission and D-dimer testing, serum creatinine levels, diagnoses including type of TED and type of renal dysfunction (defined as acute, chronic, and/or "acute on chronic"), history of TED, history of recent operation and immobility, infection, history of cancer, presence of cardiac failure, any medication that would influence coagulation cascades, and outcome data (admission to ICU and inhospital mortality). Diagnoses were based on ICD-10 coding (9, 10). Trained personnel of our hospitals' medical coding division assessed all patients' medical records including laboratory and radiologic findings to code respective diagnoses for each individual patient.

D-Dimer Assay

D-dimer levels were assessed by the accredited hemostaseologic laboratory of the University Hospital Bern (testing matrix: citrate). The following test was used: Sysmex CS-5100 with Innovance D-dimer essay (Siemens Healthcare, Zurich, Switzerland; reference range: < 500 µg/L; sensitivity,

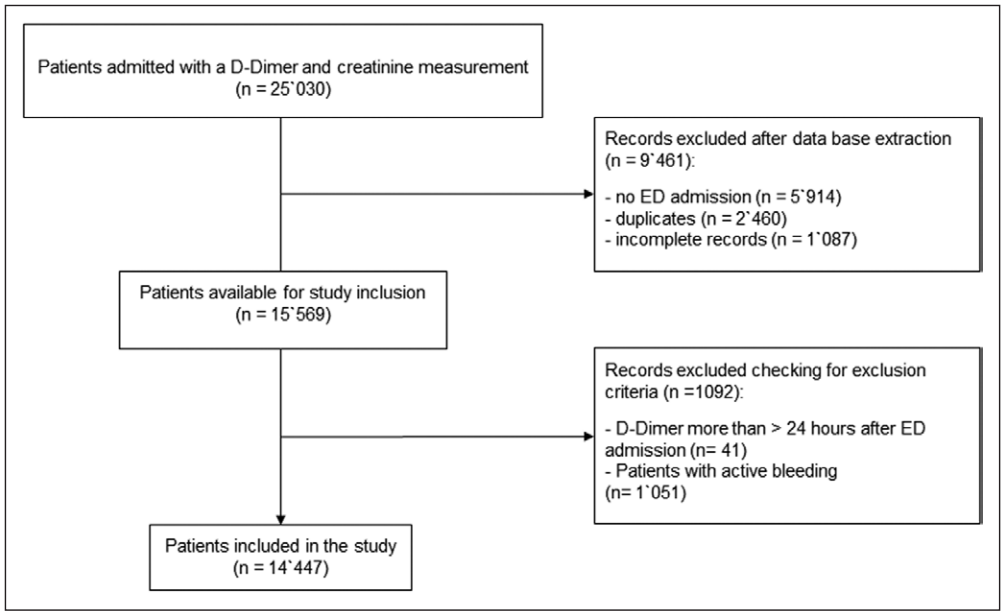

Figure 1. Study flowchart. ED = emergency department.

98.9%; specificity, 39.6%; negative predictive value [NPV], 99.6% [11]).

Serum Creatinine Assessment

Serum creatinine levels were determined from heparinized blood at the accredited Center of Laboratory Medicine, University Hospital Bern, by the use of Roche Modular P800 (F. Hofmann-La Roche, Basel, Switzerland; reference range: man, 60–104 µmol/L; woman, 45–84 µmol/L).

Definitions

TED. Patients with evidence for the following diagnoses (based on ICD-10 coding) were coded as TED: patients with PE, patients with deep venous thrombosis (DVT), and/or others (included venous thrombosis of the spleen, thrombosis of the vena porta, the vena cava, venous mesenterial thrombosis, and sinus venous thrombosis). The category DVT compromised DVT of the upper and lower extremities as well as the pelvis.

eGFR Calculation. eGFR was calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration Formula (12):

$$\mathrm{GFR} = 141 \times \min\left(\mathrm{Scr}/\kappa,1\right)^{\alpha} \times \max\left(\mathrm{Scr}/\kappa,1\right)^{1.209} \times \mathrm{Age}^{0.0993} \times 1.018\ (\text{if woman}) \times 1.160\ (\text{if black})$$

where Scr is the serum creatinine (mg/dL), κ is 0.7 for women and 0.9 for men, α is –0.329 for women and –0.411 for men, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Assessment of Renal (Dys)function. The grading of renal function was based on eGFR estimates (see above) (13). For this study and in accordance with our previous investigation (8), a simplified grading system was used to assess three key categories of renal dysfunction: eGFR less than 30 mL/min/1.73 m^2 (severe renal dysfunction), eGFR 30–60 mL/min/1.73 m^2 (moderate renal dysfunction), and eGFR greater than 60 mL/min/1.73 m^2 (normal renal function or mild renal dysfunction).

Definition of Renal Dysfunction. The assessment of whether a given patient had acute, chronic, and/or "acute on chronic" renal dysfunction was based on respective established ICD-10 diagnoses. The ICD-10 coding system bases its definition of chronic kidney disease on the grading by the Renal Association (13). The grading in the ICD-10 code for acute kidney injury follows the RIFLE criteria (14, 15). Patients with "acute on chronic" renal dysfunction were defined as patients with a known history of chronic kidney disease with acute aggravation.

Comparison of D-Dimer Cutoff Levels

We compared the "conventional" D-dimer cutoff level of 500 µg/L (3) with the eGFR-adjusted D-dimer cutoff levels as previously proposed by our group (8). For adjusted cutoff levels, we used greater than 333 µg/L for the eGFR group greater than 60 mL/min/1.73 m^2, greater than 1,306 µg/L (eGFR, 30–60 mL/min/1.73 m^2), and greater than 1,663 µg/L (eGFR, < 30 mL/min/1.73 m^2). Adjusted cutoff levels were calculated to obtain a posttest probability of 1%, a widely accepted safety benchmark for patients with TED (16).

Ethical Considerations

The study was approved by the competent Ethics Committee of the Canton of Bern (Kantonale Ethikkommission [cantonal ethics committee (EC) in German]), Switzerland (EC no. 2018-00560). Individual informed consent was waived by the EC.

Statistical Analysis

Stata 13.1 (StataCorp, The College Station, TX) was used for statistical analysis.

For descriptive purposes, medians with interquartile (25–75th quartile) ranges are given. For continuous variables, absolute values accompanied by the relative number are presented. As most variables were not normally distributed, log transformation and nonparametric testing was applied. The Spearman rank correlation test was used to test for a correlation among eGFR, serum creatinine levels, and D-dimer levels.

To quantify diagnostic strength, sensitivity/specificity, and negative and positive predictive values are given for the unadjusted and adjusted D-dimer levels in the respective subgroups. A two-tailed p value of less than 0.05 was considered significant.

RESULTS

Of 19,116 patients, a total of 14,477 patients were available for study inclusion (Fig. 1).

Patient Characteristics

The median age was 64 years (interquartile range [IQR], 49–77); 52.6% (n = 7,613) of the patients were men. A total of 467 patients (3.5%) had TED with PE being the most frequent presentation of TED (n = 302 [64.6%]). Median D-dimer levels were 509 µg/L (IQR, 268–1,196 µg/L) (**Table 1**). The median serum creatinine level was 76.0 µmol/L (IQR, 64–91 µmol/L), and the median was eGFR 100 mL/min (IQR, 71–141 mL/min). Of respective patients, 82.4% (n = 11,935) presented with an eGFR greater than 60 mL/min/1.73 m^2. A total of 1,364 patients (9.4%) had chronic kidney disease; acute kidney injury was present in 228 (1.6%) of all patients. **Supplemental Digital Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/F284) shows the association of thromboembolia (TE) with baseline/patient characteristics: a significant association ($p < 0.001$) was observed with age, previous TE, chronic and acute renal failure, cardiac insufficiency, acute infection, solid and hematologic neoplasia, and prior surgery.

D-Dimer Levels and Renal (Dys)function

Declining eGFR moderately correlated with D-dimer levels (Spearman ρ, –0.33; $p < 0.0001$), whereas creatinine values and D-dimer levels correlated weakly (Spearman ρ, 0.22; $p < 0.0001$) (**Fig. 2**). The association between renal dysfunction and negative D-dimer values is given in Table 1. With

TABLE 1. D-Dimer and Renal (Dys)function

Renal Dysfunction/Renal Insufficiency Grade	Patients, *n* (%)	D-dimer <500 µg/L, *n* (%)	Thromboembolic events, *n* (%)
Renal function (mL/min)			
eGFR > 60	11 935 (82.4)	6,574 (55.1)	353 (3.0)
eGFR 30–60	1,919 (13.3)	477 (24.9)	94 (4.9)
eGFR < 30	623 (4.3)	73 (11.7)	53 (8.5)
Renal insufficiency			
Kidney failure, any type	1,364 (9.4)	191 (14.0)	123 (9.0)
Chronic kidney failure, any stage	1,253 (8.7)	176 (14.0)	113 (9.0)
Acute kidney failure, any stage	228 (1.6)	26 (11.4)	24 (10.5)
Acute on chronic, kidney failure	117 (0.8)	11 (9.4)	14 (11.9)

eGFR = estimated glomerular filtration rate.

declining renal function, the percentage of patients with a D-dimer below the conventional cutoff of less than 500 µg/L decreased from 55.1% (eGFR, > 60 mL/min/1.73 m^2) to 11.7% (eGFR,< 30 mL/min/1.73 m^2).

Out of 1,364 patients with acute kidney injury, chronic renal failure, or "acute on chronic" renal dysfunction (any type), 86.0% of patients had D-dimer levels greater than 500 µg/L, whereas 9.0% had a thromboembolic event.

Comparison of Test Characteristics

Supplemental Digital Table 2 (Supplemental Digital Content 2, http://links.lww.com/CCM/F285) indicates test characteristics for the conventional D-dimer cutoff of 500 µg/L and eGFR-adjusted D-dimer cutoffs. When eGFR-adjusted D-dimer cutoff levels are used for TED testing, respective test characteristics were considered comparable (NPV 99% and similar sensitivity/specificity). In patients with eGFR 30–60 mL/min/1.73 m^2, the number of false positives was reduced by 49.9% (675/1,353), whereas in the eGFR group less than 30 mL/min/1.73 m^2, this number was reduced by 55.8% (278/498) when adjusted cutoff values were used.

Sensitivity Analysis

When eGFR-adjusted D-dimer cutoff levels are used in patients with acute kidney injury, the NPV remained high (98.8%) with a sensitivity of 95.8% and a specificity of 39.2%. The same was observed for patients with "acute on chronic" renal dysfunction, where the use of renal function–adjusted D-dimer values showed a sensitivity of 98.0%, a specificity of 48.5% with a NPV of 98.0%. Test characteristics for eGFR-related D-dimer cutoff levels in patients with acute and/or "acute on chronic" renal dysfunction are given (Supplemental Digital Table 2, Supplemental Digital Content 2, http://links.lww.com/CCM/F285). Test characteristics remained comparable when data were stratified by gender and age groups (**Supplemental Digital Table 3**, Supplemental Digital Content 3, http://links.lww.com/CCM/F286).

DISCUSSION

This single-center retrospective study aimed to validate previously suggested eGFR-dependent D-dimer cutoff levels (8) to exclude TED in critically ill patients. Furthermore, we aimed to evaluate a potential influence of a specific type of renal dysfunction on the ability of adjusted D-dimer cutoff levels to exclude patients with TED. We observed that the use of eGFR-adjusted D-dimer cutoff levels appeared safe to rule out TED in critically ill patients admitted for suspected TED. Furthermore, an influence of the type of renal dysfunction on test performance was not observed.

Apart from previous studies by our group (7, 8), only two other studies evaluated the use of renal (dys)function on adjusted D-dimer cutoff levels (6, 17). One study investigated 1,784 ED patients with mild to moderate renal dysfunction (17) and confirmed the safety of renal function–adjusted D-dimer thresholds. In contrast, a recently published study from Germany involving 1,082 patients questioned the validity of renal function–adjusted D-dimer testing in individuals suspected for venous thromboembolism (6). However, the results of the latter study may need to be interpreted with caution and respective data can likely not be compared with our investigation for several reasons. First, the patient population had a rather high prevalence of TED with almost half of the patient population being diagnosed with TED (6). In contrast, our current and previous data may reflect rather typical prevalence rates of thromboembolic events of about 2–5% (18–20). Second, the data presented in the German trial originated from a large prospective study investigating patients with DVT and/or PE (21). This might have introduced a selection bias as inclusion criteria for this study were either "proven" or suspected TED, and patients were recruited based on these inclusion criteria on all hospital wards (21). In contrast, we aimed to include all patients admitted to the ED with "suspected" thromboembolic events. Third, median D-dimer values were 1,400 µg/L (IQR, 3,120 µg/L) in the German study, whereas they were 509 µg/L (IQR, 928 µg/L) in our study. This may implicate that a considerable number of patients with a high pretest probability

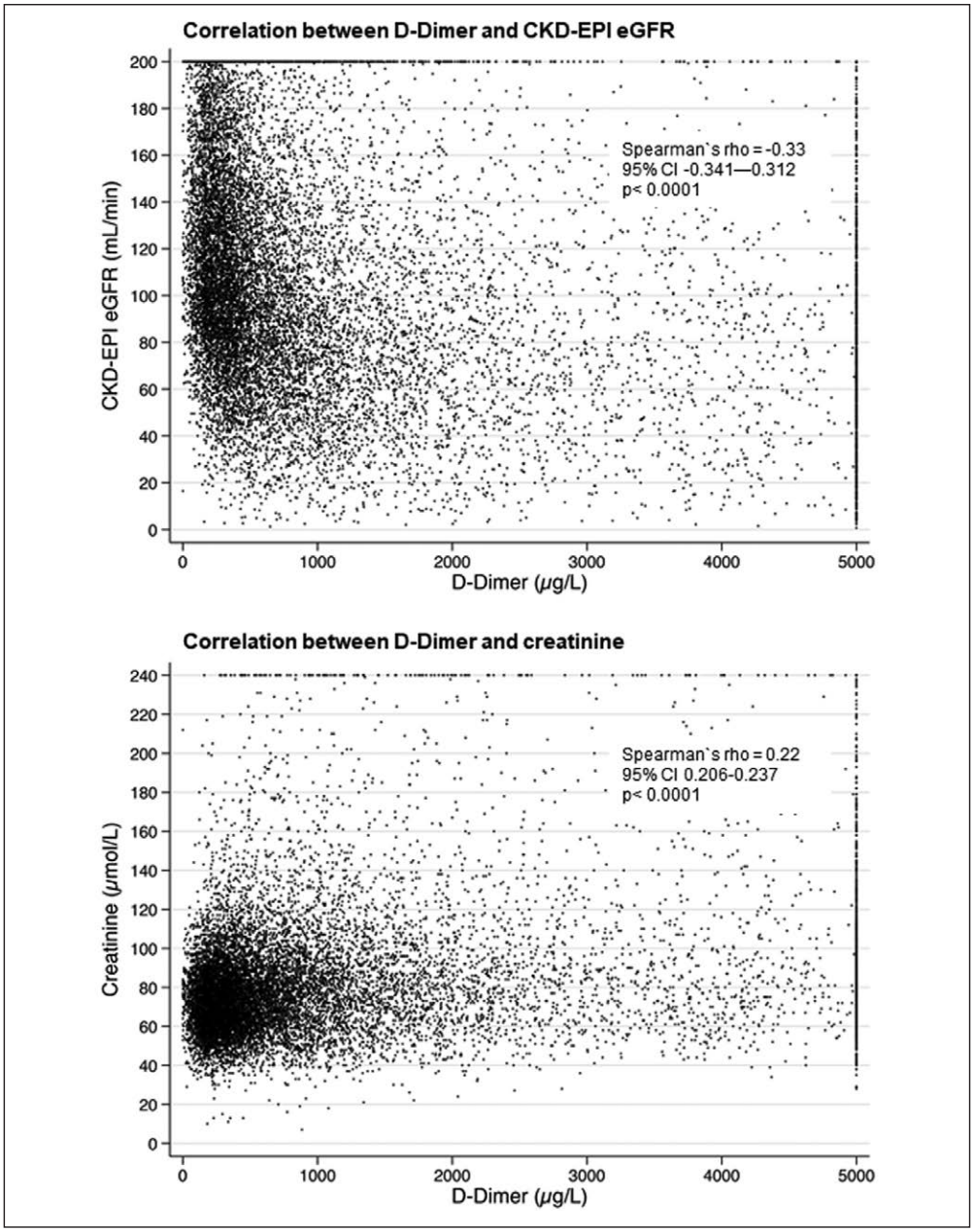

Figure 2. Correlation between D-dimer/estimated glomerular filtration rate (eGFR) and serum creatinine/D-dimer. CKD-EPI = Chronic Kidney Disease Epidemiology.

for TED (or proven TED) was likely included in this study cohort. D-Dimer testing, independent of whether adjusted or conventional cutoff levels were applied, may not be regarded optimally suited for a population with a high pretest probability or in patients already diagnosed with TED (3). Fourth, the significantly lower percentage of patients with severe renal dysfunction in the German study (2.6% vs 4.6% in our study) might hamper comparison and drawing of further conclusions as this appeared to be the patient group that might benefit the most from adjusted D-dimer cutoff testing.

A particular strength of adjusted cutoff levels may be the significant (almost 50%) reduction in the number of false positives in the moderate to severe renal dysfunction group. This may be considered of major importance, as exposure to contrast media used for CT-pulmonary angiography and resulting associated contrast-induced nephropathy is regarded of considerable prognostic importance in this cohort of patients and should be avoided whenever possible (22, 23). eGFR-adjusted cutoff levels may also allow for exclusion of TED and avoidance of radiologic workup in patients with moderate to severe renal dysfunction with a low to moderate pretest probability. Notably, in our population, 86% (1,173/1,364) of all patients with renal dysfunction had a D-dimer measurement above the conventional D-dimer cutoff of 500 µg/L, whereas 9% (123/1,364) of those patients effectively suffered from TED. Hence, radiation exposure might be avoided and healthcare costs reduced when eGFR-adapted D-dimer thresholds are applied.

It seems not surprising that for patients in the eGFR greater than 60 mL/min/1.73 m^2 group, the number of false positives rises when the adjusted cutoff value of 333 µg/L is applied compared with the conventional cutoff. However, as this is a rather large cohort of patients, the issue of false positives may still remain problematic. The high number of false positives may relate to additional factors (other than renal dysfunction) that may influence the coagulation cascade and hence result in increased D-dimer levels including age, pregnancy, systemic infection, active malignancy, surgery, immobility, or others (6–8, 24–26). Until now, studies investigated adjustment for single confounders when evaluating patient-adjusted D-dimer thresholds. In consideration of the complex pathophysiology of D-dimers and many contributing factors leading to rise in blood levels, the potential of adaptation to multiple patient-specific factors seems tempting.

Theoretically, if eGFR-based D-dimer thresholds would have been applied in January 2014, further radiologic workup might have been omitted in 884 patients, with 18 patients theoretically having a delayed or missed diagnosis. However, while evaluating new test thresholds, it appears that there

obviously is inevitable trade-off between false positives and false negatives. Due to the potential high mortality associated with TED, a low safety margin of 1–2% may be deemed appropriate (16). Hence, the aim for further improvement of D-dimer test characteristics may lie in keeping the safety margin while improving test specificity. Individualizing the cutoff value based on the patient's individual attributes (e.g., age, pregnancy) and disease profile (e.g., renal dysfunction) might considerably reduce the number of false positives in patients admitted with TED. Potentially, further "individualizing" of D-dimer thresholds taking into account multiple confounding factors for increased D-dimer might improve the specificity of (individualized) thresholds while maintaining a safety margin of about 1%.

This is the first study to evaluate the use of eGFR-dependent D-dimer thresholds for the exclusion of TED in patients with acute and "acute on chronic" renal dysfunction. Hence, we evaluated the use of eGFR-adjusted D-dimer cutoff levels in these patient groups. Our results imply that eGFR-adjusted D-dimer thresholds can be used safely for the exclusion of TED in patients admitted with acute or acute on chronic kidney disease, provided that eGFR (CKD-EPI) is calculated based on serum creatinine levels within 24 hours of ED admission. This seems important for clinicians, as baseline eGFR or creatinine values are often not known in patients admitted to the ED and thus differentiation among acute, chronic, and "acute on chronic" renal dysfunction in a timely manner can be particularly challenging. Nevertheless, our date indicate that, the cutoff levels proposed may be useful independent of the "type" of renal dysfunction.

In the future, further research on individualizing D-dimer cutoffs should be undertaken to especially increase the accuracy in patients later transferred to ICUs. Individual D-dimer threshold adjustment based on individual patient profiles might be especially suited for complex environments such as the ICU. Over time on the ICU, patients often suffer from multiple comorbidities and currently used "conventional" D-dimer thresholds may be limited due to confounders associated with critical illness. Special emphasis might be necessary with regard to integrating multiple patient-adjusted factors to compute individual D-dimer thresholds aiming to reduce false positives while keeping false-negative rates at 1%. Furthermore, safety and feasibility of single- or multiple-factor–adjusted D-dimer threshold should be confirmed in prospective, preferably multicenter studies.

Our study has limitations that warrant discussion. First, this is a single-center study and external validity is limited. External validity should thus be evaluated in prospective studies. Furthermore, due to the retrospective study design and a large dataset, potential false reporting/false coding and/or misclassification may have occurred. Furthermore, the specific type of TED that was suspected at ED admission was not available. Second, a D-dimer test may have been ordered without appropriate indication (additional testing), and, by nature of the retrospective investigation, documentation errors cannot be excluded with certainty. Third, despite the fact that clinical scores for assessment of pretest probability are used at our ED in daily practice, these could not be assessed electronically for this big data project and were not evaluated in this study. Fourth, this analysis assesses the diagnostic performance of eGFR-adjusted D-dimer thresholds in patients with acute, chronic, and "acute on chronic" renal dysfunction within the first 24 hours of admission. The use of eGFR-adjusted cutoffs outside this time frame requires further validation and should therefore be applied with caution. Fifth, the calculation of eGFR is based on the assumption that eGFR would remain stable within the first hours after ICU admission in patients with TED.

CONCLUSIONS

In a large cohort of critically ill patients with suspected thromboembolism, we find that renal (dys)function–adjusted D-dimer cutoffs levels appear feasible and safe (when compared with conventional D-dimer cutoffs) to assess TED. In patients with moderate or severely reduced eGFR (< 60 mL/min/1.73 m^2), the number of false positives can be remarkably reduced when adjusted cutoff values are used. Furthermore, our data suggest that eGFR-adjusted D-dimer cutoff values appear also reliable in patients with acute and/or "acute on chronic" renal dysfunction. Confirmatory prospective investigations seem warranted.

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Drs. Schefold and Gerber contributed equally to this work.

Dr. Gerber and Ms. Angehrn assessed the data. Dr. Müller provided statistical advice on study design and analyzed the data. Drs. Schefold, Gerber, and Pfortmueller drafted the article. Ms. Angehrn, Dr. Müller, Dr. Messmer, and Dr. Exadaktylos revised the article for important intellectual content. Dr. Pfortmueller conceived the study and designed the trial, and supervised the conduct of the trial and data collection. All authors read and approved the final draft.

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