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The Provision of Thromboprophylaxis and the Prediction of Renal Recovery in Critically Ill Patients with Acute Kidney Injury

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Abstract

Background: It is unknown whether the dose of enoxaparin can be optimised, without increasing the risk of bleeding, in critically ill patients with acute kidney injury (AKI). Neutrophil gelatinase-associated lipocalin (NGAL) is associated with AKI, and the subsequent need for continuous renal replacement therapy (CRRT). The predictive value of plasma and urine NGAL for renal recovery is not established.

Methods: A double-blinded randomized trial was conducted in medico-surgical intensive care units across Denmark to establish markers of renal recovery, and to determine whether a dose of 1 mg/kg enoxaparin once daily (QD) would improve thromboprophylaxis. Patients were randomly assigned to receive 1 mg/kg enoxaparin QD or 40 mg enoxaparin QD upon commencement of CRRT. The primary outcome was the occurrence of venous thromboembolism (VTE). Secondary outcomes included major bleeding, NGAL levels and urine output.

Results: Poor accrual led to early study closure after enrolment of only 19 patients. Patients were comparable with respects to baseline demographics, the interval prior to start of dialysis, and the duration of dialysis. No episodes of VTE or of major bleeding occurred. During the dialysis-free interval, plasma NGAL levels were higher in non-renal recovery (1074 [± 694] ng/mL) compared to renal recovery patients (296 [± 197] ng/mL; $P = 0.01$), and urine NGAL levels were higher in non-renal recovery (3885 [± 2722] ng/mL) compared to renal recovery patients (597 [± 565] ng/mL; $P = 0.006$). Multiple regression analysis showed that only urine NGAL could independently predict recovery from AKI ($P = 0.006$).

Conclusion: Our study did not recruit enough patients to test the hypothesis that 1 mg/kg enoxaparin QD could safely improve thromboprophylaxis. However the study suggests that urine NGAL may be able to predict renal recovery in critically ill patients, and allow proper utilization of resources. (EU Clinical Trials Register EudraCT Number: 2012-004368-23; URL: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-004368-23/DK>).

Keywords: Thromboprophylaxis; ICU Patients; Acute kidney injury; Continuous renal replacement therapy; Neutrophil gelatinase-associated lipocalin; Renal recovery

List of abbreviations

Activated Partial Thromboplastin Time (aPTT), Acute Kidney Injury (AKI), Acute Kidney Injury Network (AKIN), Acute Physiology and Chronic Health Evaluation (APACHE), Antifactor Xa (anti-Xa), Antithrombin (AT), Area Under the Curve (AUC), Biological Markers of Recovery for the Kidney (BioMaRK), Continuous Renal Replacement Therapy (CRRT), Creatinine (Cr), Delayed Graft Function (DGF), Feasible Strategy for Preventing Blood Clots in Critically Ill Patients with Acute Kidney Injury (FBI), Good Clinical Practice (GCP), Heparin-Induced Thrombocytopenia

(HIT), Intensive Care Unit (ICU), International Normalized Ratio (INR), Low-Molecular-Weight Heparin (LMWH), Neutrophil Gelatinase-Associated Lipocalin (NGAL), Number (N), Once daily (QD), Randomized Controlled Trials (RCTs), Sequential Organ Failure Assessment (SOFA), Subcutaneous (sc), Tissue Inhibitor of Metalloproteinases-2 (TIMP-2), Unfractionated Heparin (UFH), Urine Insulin-Like Growth Factor-Binding Protein 7 (IGFBP7), Venous Thromboembolism (VTE)

Background

Approximately 30 % of critically ill patients admitted to an intensive care unit (ICU) develop acute kidney injury (AKI) [1]. Biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) are associated with AKI and the subsequent need for dialysis [1-4]. The risk of venous thromboembolism (VTE) among ICU patients receiving prophylactic low-molecular-weight heparin (LMWH) was found to be 5-15.5% [5,6]. The presence of AKI is said to further increase this risk by as much as four-fold [7-9]. Randomized controlled trials (RCTs) for thromboprophylaxis comparing LMWH with unfractionated heparin (UFH), found no significant difference in the rate of proximal leg deep venous thrombosis, or of bleeding with the use of LMWH [6,10,11]. Our previous RCT showed that a weight-based dose of enoxaparin subcutaneous (sc) once daily (QD) yielded satisfactory levels of antifactor Xa activity (anti-Xa) for critically ill patients, was more likely to maintain anti-Xa, and did not result in bioaccumulation [12]. The primary objective of this study was to reduce the incidence of VTE among critically ill AKI patients by using 1 mg/kg enoxaparin sc QD, versus the standard dose of 40 mg enoxaparin sc QD. Secondary objectives of the trial included examining the utility of NGAL levels and urine output as predictors of renal recovery in critically ill patients.

Methods

The feasible strategy for preventing blood clots in critically ill patients with acute kidney injury (FBI) trial commenced recruitment in Danish ICUs in March 2013. Patients were eligible for inclusion if they consented, developed AKI, needed continuous renal replacement therapy (CRRT), weighed 45 - 150 kg, and were ≥18 years. AKI was defined according to Acute Kidney Injury Network (AKIN) criteria. Exclusion criteria included a) admission diagnosis of major trauma, b) need for therapeutic anticoagulation, c) contraindication to heparin: allergy or heparin-induced thrombocytopenia (HIT), d) pregnancy, e) life-support limitation, f) uncontrolled hypertension (blood pressure > 180/110) for at least 12 hours, g) cerebral hemorrhage or acute gastrointestinal bleeding, h) severe thrombocytopenia (platelet count < 50 × 10⁹/l), i) International Normalized Ratio (INR) or activated partial thromboplastin time (aPTT) ≥ 2 times the upper limit of normal,

j) chronic renal failure or acute-on- chronic renal failure, and k) initial evaluation after more than 24 hours had elapsed from commencement of CRRT.

We randomly assigned patients into a treatment (1 mg/kg enoxaparin sc QD) or a control arm (40 mg enoxaparin sc QD) upon commencement of CRRT. Research coordinators obtained written informed consent from all patients or their designated surrogates.

We recorded patient demographics, diuresis, and standard ICU severity of illness scores. Patients underwent daily bedside clinical assessment for bleeding or VTE using validated tools [13-15]. Patients were evaluated with compression ultrasound, and anti-Xa levels were measured. Urine and plasma NGAL were measured at baseline and during CRRT-free intervals.

The primary outcome was the occurrence of VTE. Secondary outcomes included anti-Xa activity, major bleeding, HIT, and length of stay. In addition, we monitored NGAL levels and urine volume to determine whether they could be used as prognostic factors for renal recovery.

A detailed description of project FBI's definitions, the conduct of CRRT, schedule for clinical examination and drawing of blood samples, data collection, and management strategies has been described elsewhere [16].

We estimated that with 133 patients in each group, the study would have 80% power to show a 40% reduction in the relative risk of VTE with 1 mg/kg enoxaparin sc QD, assuming an incidence rate of 40% in the control group, at a two-sided alpha level of 0.05.

All baseline demographic values for these two groups were compared using the Student's t-test or Mann-Whitney rank sum test for continuous variables, and Fisher's exact test for categorical variables. The prediction ability of urine output and NGAL for successful discontinuation of CRRT was assessed with multiple regression analysis. We analyzed data from all patients according to their assigned group (intention-to-treat principle).

The trial was approved by the Danish national scientific ethical committee (reference number: 1210528) and the Danish health and medicine authority (reference number: 2012100176). The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki, and monitored by Good Clinical Practice (GCP).

Results

The study was closed in early February 2015-a decision made in conjunction with GCP and the project's data monitoring committee-owing to poor accrual despite intense efforts to increase recruitment. Of the AKI patients admitted to the ICU during the study period, 17.8% were excluded due to use of therapeutic anticoagulation, 16.3% due to hemorrhage on ICU admission, 14.1% due to low platelet count/coagulopathy, 12.5% due to limitation of life support, and 11.1% due to chronic renal failure/acute-on-chronic failure. In addition, the majority of ICUs in Denmark started using regional citrate as the standard anticoagulant during dialysis, and this further thwarted efforts to increase recruitment. 10 patients were assigned to receive enoxaparin 40 mg, and 9 patients to receive enoxaparin 1 mg/kg. Patients in both enoxaparin groups were well matched at baseline (Table 1). There were no episodes of major bleeding or of VTE. Two patients -1 from each enoxaparin group- developed HIT.

Peak anti-Xa was 0.47 IU/ml for 1 mg/kg enoxaparin compared to 0.16 IU/ml for 40 mg enoxaparin ($P = 0.17$). Trough anti-Xa was 0.14 IU/ml for 1 mg/kg enoxaparin compared to 0.003 IU/ml for 40 mg enoxaparin ($P = 0.05$). Patients in the group that received 40 mg enoxaparin needed higher doses of regional UFH during CRRT (Table 1), and five patients in that group compared with none in the group that received 1 mg/kg enoxaparin needed regional citrate ($P = 0.03$).

The main cause of AKI was sepsis or septic shock (42%). In 63% of the patients, the reason for starting dialysis was either anuria or electrolyte disturbances. 26% of patients were dialysis-dependent after the first dialysis-free period on the ICU. Patients were comparable with respect to the interval prior to start of dialysis, and the duration of dialysis (Table 2).

Once patients achieved diuresis of > 200 ml/day on CRRT, dialysis was discontinued. During the dialysis -free interval, the mean urine volume was similar in non-renal recovery and renal recovery patients (Table 2). However, non-renal recovery patients needed far higher doses of furosemide (371.5 mg), when compared with renal recovery patients (103 mg; $P = 0.05$) to maintain comparable urine volumes. The number of patients needing vasopressors did not differ significantly between the renal recovery

Enoxaparin Dose	1 mg/kg N = 9	40 mg N = 10	P value
Gender(m:f)	7:2	7:3	1.00
Mean age (years)	57.6 ± 14.2	62 ± 10.3	0.44
Mean weight (kg)	87.1 ± 20.6	92.5 ± 24.7	0.62
APACHE II	26.9 ± 10.4	27.3 ± 5.1	0.91
SOFA	10.4 ± 4.1	11.2 ± 4.2	0.68
Length of stay on the ICU (days)	9.6 ± 11.2	11.6 ± 10.8	0.69
Number of patients with minor bleeding	4	4	1.00
Renal Recovery: Repeat Dialysis	8:1	6:4	0.30
Number of filters used	4.3 ± 5	3.6 ± 2	0.68
Dose of UFH (IU)	211 ± 342	845 ± 900	0.06
Number of patients who needed regional citrate	0	5	0.03
Highest aPTT in the study period (seconds)	80.4 ± 20	64.2 ± 51	0.41
Lowest platelet count in the study period ($\times 10^9/L$)	133 ± 80	130 ± 118	0.95
AT (%)	60 ± 0	86 ± 26	0.28
Duration of CRRT (hours)	86.0 ± 109	79.4 ± 45.3	0.86

Table 1: Clinical characteristics of the study population

(Values are numbers, or means ± SD; N denotes number; APACHE II denotes Acute Physiology and Chronic Health Evaluation SOFA denotes Sequential Organ Failure Assessment score; ICU denotes intensive care unit; UFH denotes unfractionated heparin aPTT denotes activated partial thromboplastin time; AT denotes antithrombin)

Renal Recovery	Success N = 14	Repeat Dialysis N = 5	P value
MAP (mm Hg)	83 ± 13	93 ± 13	0.18
Initial plasma creatinine (umol/l)	345 ± 228	354 ± 106	0.93
Initial plasma NGAL (ng/ml)	731 ± 657	881 ± 472	0.65
Initial urine NGAL (ng/ml)	3277 ± 2607	3863 ± 2470	0.67
Time to initiation of CRRT after admission (days)	1.0 ± 1.3	1.6 ± 1.5	0.35
Duration of CRRT (hours)	81.6 ± 87	84.1 ± 51	0.95
Dose of furosemide (mg)	103 ± 207	371.5 ± 350	0.05
Urine volume (ml)	731 ± 931	826 ± 950	0.85

Table 2: Baseline variables and treatment details for CRRT

(Values are numbers, or means ± SD; CRRT denotes continuous renal replacement therapy; N denotes number; MAP denotes mean arterial pressure; NGAL denotes neutrophil gelatinase-associated lipocalin)

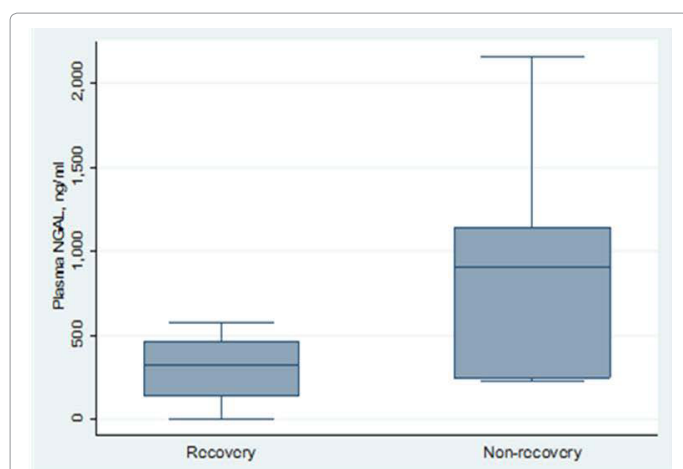


Figure 1: Plasma neutrophil gelatinase-associated lipocalin concentration by recovery

Plasma neutrophil gelatinase-associated lipocalin (NGAL) levels in critically ill patients with acute kidney injury (AKI) categorized into non-renal recovery and renal recovery groups.

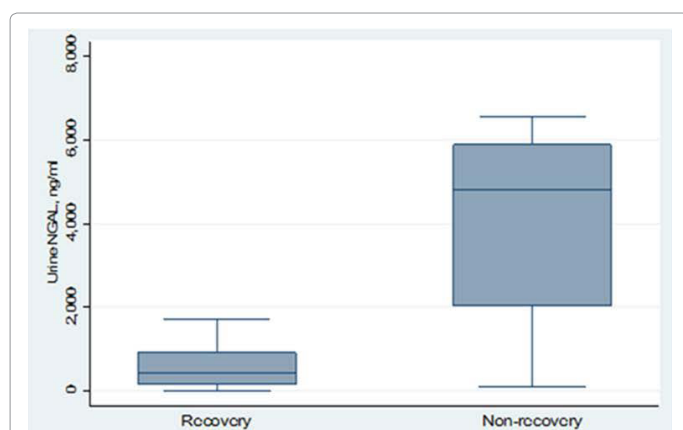


Figure 2: Urine neutrophil gelatinase-associated lipocalin concentration by recovery

Urine neutrophil gelatinase-associated lipocalin (NGAL) levels in critically ill patients with acute kidney injury (AKI) categorized into non-renal recovery and renal recovery groups.

and non-renal recovery groups ($P = 1$), mean arterial pressure was not significantly different ($P = 0.18$), and patients had similar fluid balances before CRRT was discontinued ($P = 0.4$).

Plasma NGAL levels were higher in non-renal recovery (1074 [± 694] ng/mL) compared to renal recovery patients (296 [± 197]

ng/mL; $P = 0.01$) during the dialysis-free interval (Figure 1). Urine NGAL levels were higher in non-renal recovery (3885 [± 2722] ng/mL) compared to renal recovery patients (597 [± 565] ng/mL; $P = 0.006$) during dialysis-free interval (Figure 2). Though both plasma and urine NGAL levels appear to be significantly related to renal recovery, multiple regression analysis showed that only urine NGAL could independently predict recovery from AKI ($P = 0.006$). The number of patients with sepsis was evenly distributed between non-renal recovery and renal recovery groups ($P = 0.6$). Inflammatory parameters (white blood cell counts, C-reactive protein, and procalcitonin) did not differ significantly between the renal recovery and non-renal recovery groups.

Discussion

Our study did not recruit enough patients to test the hypothesis that 1 mg/kg enoxaparin QD would improve thromboprophylaxis without increasing bleeding. However, FBI is one of the first studies to demonstrate urine NGAL level as an independent predictor of recovery from AKI in critically ill adults.

ICU patients with AKI frequently have increased tissue factor and fibrinogen levels, as well as activation of endothelial surfaces and thrombocytes. Vascular access, along with commencement of CRRT, adds to VTE risk. Such patients are also predisposed to bleeding because of thrombocytopenia, coagulopathies, and comorbidities [13,17]. Thrombocytopenia, a policy of non-sedation at our institutions, and the mobilization of CRRT patients on a daily basis, are possible factors that may account for the absence of VTE events in our study, but a greater factor is likely to be the small sample size.

Conventional target peak anti-Xa levels for thromboprophylaxis in a general ward population are 0.1- 0.40 IU/ml [18,19]. The difference in peak anti-Xa between enoxaparin groups was not found to be significant, and this is again most likely due to small sample size, as our previous RCTs with approximately 80 patients each, were both able to demonstrate a significant difference in anti-Xa levels with varying doses of enoxaparin. As expected, use of CRRT prevented bioaccumulation, and consequently prevented major bleeding. Isla et al found that enoxaparin passes through the polysulfone membranes used in CRRT [20]. This is consistent with the fact that the molecular weight of enoxaparin is far lower than the cut-off for polysulfone membranes like the ones used in project FBI (cut-off: 40 - 50 kDa). Critically ill patients also have decreased levels of protein giving rise to a larger free fraction of enoxaparin available for hemofiltration.

The efficacy of CRRT depends on the continued patency of the extracorporeal circuit. Anticoagulation of the circuit is generally required to prevent clotting. During the last 2 years, the majority of ICUs in Denmark have switched from regional UFH to regional citrate

for anticoagulation of the circuit. Though citrate anticoagulation is associated with a lower risk of bleeding and longer haemofilter patency, it is a more complex and demanding system which necessitates frequent monitoring of electrolytes, ionized calcium, and acid-base status to prevent metabolic derangements [21-23].

In the FBI trial, patients who received 40 mg enoxaparin had a trend towards needing higher doses of regional UFH, and some of these patients had to be converted to regional citrate during CRRT. Our study seems to suggest that adequate anticoagulation of the circuit may be achieved by the provision of an adequate dose of systemic enoxaparin, thus reducing the need for regional UFH, and potentially negating the need for regional citrate. Antithrombin (AT) levels are often depleted in critically ill patients due to increased consumption and decreased production from liver. Subnormal levels of AT may result in heparin resistance, and may therefore influence filter performance [24]. However, there was no significant difference in AT levels between enoxaparin groups.

The patency of the dialysis circuit is also affected by severity of illness scores, platelet count, filter characteristics, and the CRRT treatment prescribed (blood flow, filtration fraction) [24-29]. In FBI, CRRT treatment was protocolised, and patients had similar platelet counts, and APACHE and SOFA scores. A polyethersulfone or polysulphone filter was used during CRRT treatments.

At present, no uniform definition for recovery after AKI exists. Renal recovery as defined in this protocol refers to the complete independence from renal replacement therapy after dialysis was discontinued. Authors have suggested that combining biomarkers and clinical variables is the most predictive model for renal injury, and so we wondered if this could be true for renal recovery. Thus we sought to use a combination of a clinical indicator (urine volume) and a biomarker (NGAL) to predict renal recovery.

Studies such as the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study identified urine production (> 400 ml/day without diuretics) retrospectively, as the best predictor for successful discontinuation of CRRT [30,31]. However our sample size was too small to validate these results.

NGAL is expressed by neutrophils and various epithelia, including the renal proximal tubules. Its production is upregulated by malignancy, infection/ inflammation, and ischemia. In AKI, plasma concentrations rise quickly, and tend to decrease quickly once the insult is resolved.

It was Bennett, et al who provided one of the earliest and largest studies linking urine NGAL to outcome. In a prospective study of 196 children undergoing elective cardiopulmonary bypass, AKI developed in 99 patients (51%), and mean urine NGAL levels increased 15-fold within 2 hours. The 2-hour urine NGAL levels correlated with severity and duration of AKI, length of stay, dialysis requirement, and death [32]. Later, other studies found that NGAL may also be an early indicator of renal recovery in critically ill patients supported by CRRT [1,2,4].

In project FBI, plasma and urine NGAL values were significantly related to renal recovery. However, the multiple regression analysis showed that only urine NGAL could independently predict recovery from AKI.

Moon, et al [33] found that urine NGAL could independently predict recovery from AKI at a cut-off value of 348ng/mL in medical patients. The Biological Markers of Recovery for the Kidney (BioMaRK) study also found decreasing urine NGAL to be associated with greater odds of renal recovery [34].

Delayed graft function (DGF) is often regarded as a type of

AKI. Hollmen, et al [35] analyzed urine samples from 176 renal transplant recipients. A total of 70 transplantations had DGF, of which 26 were prolonged. In patients who developed DGF there was a significantly slower decrease in urine NGAL compared with those who did not develop DGF. The urine NGAL level on day 1 predicted prolonged DGF (area under the curve [AUC] 0.75), which was in turn associated with significantly worse 1-year graft survival. At the optimal cut-off level of 560ng/ml, the sensitivity was 68% and the specificity was 73% [35].

In a prospective, multicenter, observational study of 91 renal transplant patients, serial urine samples after transplant were collected and analyzed. Of the patients in the cohort, 34 had DGF. On the first postoperative day, patients who had DGF had significantly higher median urine NGAL levels (1035 ng/ml) than patients who had immediate graft function (60.5 ng/ml; $P < 0.001$). Dialysis was required in 34 patients, and urine NGAL on the first postoperative day, accurately predicted dialysis within 1 week of kidney transplant, with an AUC of 0.82 [36].

As plasma NGAL concentration may also reflect production by the liver, lung or neutrophils, the elevated values seen in FBI, may not necessarily be associated solely with AKI, and this may have impacted on its utility as a predictor for renal recovery. This is in keeping with the study of critically ill patients with septic and non-septic AKI by Bagshaw et al, which showed that septic AKI was associated with significantly higher plasma NGAL levels compared with non-septic AKI ($p < 0.001$) [2].

There is also some controversy surrounding the effect of CRRT on the level of plasma NGAL, a 25 kDa protein. While some studies have determined that clearance by the filter in CRRT is low, and have found no evidence of intra-filter release of NGAL by neutrophils [37,38], other studies have demonstrated that NGAL can be adsorbed and filtrated with polysulfone membranes [39]. De Geus et al theorized that larger serum proteins occlude membrane pores preventing the passage of NGAL. In addition, by binding to other molecules, NGAL may exceed the cut-off limit for passage through the filter.

Our analysis of urine NGAL was in absolute concentration, and thus not normalized to urine excretion of creatinine (Cr). Though absolute concentration of urine NGAL may depend on urine output, and may thus suffer from intra-patient variability, patients in FBI's recovery and non-recovery groups had comparable urine output. In addition urine Cr excretion undergoes dynamic changes during AKI. Singer et al found that urinary NGAL levels had similar test characteristics, irrespective of whether they were corrected for urinary Cr concentrations or not [40].

Several factors make it difficult to compare our NGAL results with those from other studies. Most previous NGAL studies have focused on pediatric and adult cardiac surgical patients, and patients with contrast-induced nephropathy - patients with a known onset of AKI. In addition, there are several different techniques commercially available for the assay of NGAL [32,41,42]. Finally, different subgroups of critically ill patients may require different cut-off values of NGAL for diagnosis of AKI and for possible predictive use [43].

Our study did not recruit enough patients to test the primary hypothesis, and this is an obvious limitation. It is also possible that the characteristics of NGAL may not be the same in clinical settings. Finally, newer biomarkers such as urine insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) have recently been evaluated in the Sapphire study. The combination of these 2 markers (urine [TIMP-2] · [IGFBP7]) demonstrated an area under the curve of 0.80 for the

development of AKI within 12 hours, and may yet prove to be an important predictor of renal recovery [44]. However this new assay is expensive and not widely available.

These limitations were offset by daily screening for consecutive eligible patients, and comprehensive clinical assessment with validated tools. The randomized study groups were well matched, NGAL appears to be a robust marker of renal recovery, and the results obtained for regional citrate anticoagulation were promising. However these findings will have to be confirmed in other larger trials.

Conclusion

Our study did not recruit enough patients to test the hypothesis that 1 mg/kg enoxaparin QD would improve thromboprophylaxis. However, FBI has shown urine NGAL levels to be predictive of renal recovery in critically ill patients.

Authors' Contributions

PT conceived the research and SR, with input from PT, CE, AZ, and ULL designed the study. SR secured funding for the project, recruited and followed patients, interpreted the results, and performed the statistical analysis. AZ, ULL, and SZ assisted with patient enrolment, examination and data collection. CE assisted with the statistical analysis. MN assisted with the interpretation of the results. BR carried out the chromogenic assays. The first author wrote the first draft of the manuscript, and subsequent drafts were prepared with input from the co-authors, all of whom approved the submission of the final version of the manuscript.

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