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# Is antecedent D-Dimer testing prior to compression ultrasonography likely to be helpful for evaluating deep vein thrombosis in acute medical inpatients? A retrospective case series at a tertiary hospital

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## RESEARCH

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## ABSTRACT

**Background**
Venous thromboembolism is a preventable cause of death in hospital, D-Dimer assays are highly sensitive for detecting VTE but have not been validated in inpatients. Acute medical inpatients frequently have comorbid conditions that may limit the value of this test.

**Aim**
We aim to review the evidence regarding D-Dimer use and apply it to an acute medical inpatient cohort to determine its potential applicability in this setting.

**Methods**
A retrospective review of acute medical inpatients (within 48h of admission) was performed over a two year period who had compression ultrasonography. For patients without antecedent D-Dimer testing, medical records were reviewed to determine if a comorbid illness was present that would limit D-Dimer value. Pregnancy, active malignancy, significant infection, known arterial thrombus, VTE already detected, stage 4 CKD, age >80, exacerbation of moderate to severe COPD and clinical question of collection, not DVT, were accepted reasons that justified no D-Dimer.

**Results**
Three hundred and forty eight acute medical inpatients underwent DVT ultrasonography in this timeframe, 60 had confirmed DVT. 10.6 per cent of cases underwent antecedent D-Dimer testing, and a valid medical reason was identified in 84.9 per cent of cases who did not. Elderly age, significant infection and admission with active malignancy were the most common reasons to not proceed with D-Dimer testing.

**Conclusion**
Most acute medical inpatients proceeded straight to ultrasonography to evaluate for DVT which is largely supported by available literature. This study supports the limited, if any, role for antecedent D-Dimer use in acute medical inpatients due to their comorbid conditions.

**Key Words**
Doppler ultrasound, Deep vein thrombosis, Venous thromboembolism, D-Dimer

## What this study adds:

**1. What is known about this subject?**
D-Dimer is a sensitive marker of venous thromboembolism but has not been validated in acute medical inpatients. Their often-present comorbidities may render this test unhelpful.

**2. What new information is offered in this study?**
Acute medical inpatients present with comorbidities

significant enough to warrant not performing an antecedent D-Dimer.

**3. What are the implications for research, policy, or practice?**

The use of D-Dimer assays for acute medical inpatients is not supported by the literature and hospital guidelines should reflect this.

## Introduction

Venous thromboembolism (VTE) is a preventable cause of death of inpatients in hospitals, thus attention on the prevention, diagnosis and management of VTE remains of great importance. D-Dimer assays have a high sensitivity and a high negative predictive value for excluding VTE and have been validated in the outpatient setting,[1] however the role for its inpatient use is unclear. The current iteration of the Diagnostic Imaging Pathways guidelines does not recommend antecedent D-Dimer testing for the evaluation of lower limb deep vein thrombosis (DVT) for hospital inpatients.[2]

In addition to VTE, a number of other conditions can elevate plasma D-Dimer levels, including arterial sources of thrombus, chronic kidney disease, malignancy, infectious and inflammatory conditions and exacerbations of chronic obstructive pulmonary disease (COPD). Older age and pregnancy also cause elevations of plasma D-Dimer. These conditions are often co-existent in acute medical inpatients. Compression ultrasonography (CUS) of the lower limb(s) remains the gold standard for the diagnosis of DVT with high sensitivity and specificity.[3]

The median length of stay for medical patients at this facility is less than 2.5 days, patients admitted for longer than this usually have complex active medical or social concerns, therefore it is assumed that assessment for DVT performed beyond 48 hours of admission represents an atypical patient cohort. There is no published data on this cohort of acute medical patients. Two studies have evaluated the role of D-dimer in medical patients, however much higher D-Dimer cut-offs (0.9–1.0mg/L) were used compared to the standard reference range (0.5mg/L) and patients were studied beyond their sixth day of admission; 9.5 per cent and 24.5 per cent had a negative D-dimer according to that cut-off. It is not known how many cases had a negative D-dimer based on the standard reference range.[4,5]

This retrospective case series aims to review the role of D-dimer assays in acute medical inpatients at a tertiary hospital, by reviewing the aforementioned criteria that elevate D-dimer values, and applying evidence-based criteria that would render a D-dimer test positive in the absence of a DVT, and applying those criteria to determine the utility of this test in acute medical inpatients in a tertiary medical centre.

## Method

### Study population

After obtaining institutional review board approval, a retrospective review was undertaken. The Picture Archiving and Communication Software (PACS) system was searched and all CUS studies performed at a single tertiary hospital were retrieved from 01/01/2016 to 31/12/2017. CUS examinations performed within 48 hours of hospital admission were identified and captured in this way. Patients under the care of a surgical specialty, a critical care department or the emergency department were excluded as they represent a non-medical cohort.

Excluded referrals generated from:

- ED and ED observation unit (517)
- Outpatients (297)
- Surgical specialties (300)
- ICU/HDU (87)
- Day procedure patients* (11)
- Mental health (7)
- Obstetric hospital transfers (2)

*includes dialysis, endoscopy and day chemotherapy units

Electronic laboratory records were then reviewed to ascertain which cases underwent antecedent D-Dimer testing. Of all cases without antecedent plasma D-Dimer studies, a single author (AR) evaluated the patient medical records to identify a valid medical reason why D-Dimer testing would be potentially suitable or unsuitable. In borderline or uncertain cases, consensus decision was reached with a second author, a consultant physician experienced in acute medical care (SKS). Cases deemed inappropriate to progress with D-dimer testing are listed in Table 1. These are all conditions known to significantly elevate D-dimer in the absence of VTE.

### D-Dimer assay

The D-dimer liatest reagent (Diagnostica Stago Inc.) is a suspension of polystyrene latex particles of uniform size coated with a monoclonal antibody highly specific for the D-dimer domain included in fibrin soluble derivatives. An antigen-antibody reaction takes place, leading to an agglutination of latex micro particles which leads to increased turbidity of the reaction medium, which is reflected by an increase in absorbance which is measured

photometrically. Whole blood is drawn into 3.2 per cent tri-sodium citrate solution and centrifuged for 10 minutes at 15 degrees Celsius. Hemolyzed specimens which may interfere with the result were dis carded by the laboratory, and a repeat sample was obtained for analysis. A cut-off value of 0.5mg/L was used, in keeping with the standard reference range.

**Compression ultrasonography**

Lower limb venous duplex scanning was performed by a trained sonographer or a trainee radiology registrar, with variable years of imaging experience, and all images were overseen and interpreted by a Consultant Radiologist and reported as positive or negative for DVT. Where possible, whole leg evaluation was undertaken. Wound dressings, where present, were never removed for the examination and occasionally significant pain to ultrasound probe pressure limited the examination.

Patients admitted to a tertiary hospital with active malignancy are characteristically unwell and represent either cytotoxic treatment side effect(s) or disease progression, both of which are considered here to not warrant a D-Dimer. Cases with known VTE and arterial thrombus, are also considered to be valid reasons to not proceed to D-Dimer testing. Pregnant patients and patients immediately postpartum were also considered valid reasons.[6] To evaluate infection, chronic kidney disease and age, an English language PubMed search was undertaken with the following keyword search strategies: “D-Dimer AND age”, “D-Dimer AND infection”, “D-Dimer AND inflammation”, “D-Dimer AND renal failure”, “D-Dimer and kidney disease”, “D-Dimer and CKD” to determine a binary cutoff. Additional search strategies were undertaken for other conditions considered to elevate the D-Dimer including cirrhosis and heart failure, however these were not included due to conflicting data on the degree of influence these conditions had on D-Dimer.

## Results

A total of 1846 CUS examinations were performed in this two-year period. Following the aforementioned exclusion criteria, 626 medical inpatient cases remained and 348 (55.6 per cent) underwent CUS examinations within 48 hours of admission and was therefore included in this study. 60 cases had confirmed DVT by CUS, 12 of which underwent antecedent D-dimer testing which was positive and 48 proceeded straight to CUS.

There were 34 positive D-dimers in our group, and by our criteria, 28 had a valid reason not to warrant a D-dimer. Of the six that potentially did, four were in their late 70s, one had stage 3 CKD and the other had acute kidney injury.

In total, 311 cases (89.4 per cent) did not undergo antecedent D-dimer testing and by the previously mentioned criteria, 264 (84.9 per cent) of these had a valid reason for not pursing an antecedent D-dimer, as shown in Table 2.

Of the 47 who did not, 17 were approaching but did not reach the predefined binary criteria. A further six patients had decompensated cirrhosis or heart failure, two had rhabdomyolysis, two had severe inflammatory bowel disease proven endoscopically, and the remaining 19 had a variety of other diagnoses.

## Discussion

A relatively large number of acute medical inpatients, admitted for reasons other than the investigation of VTE, underwent investigation to exclude DVT. 90 per cent of patients in this cohort did not undergo antecedent D-dimer testing prior to proceeding to CUS. There are no prospective or retrospective studies evaluating the role of D-dimers for assessment of DVT in acute medical inpatients. Advancing age, significant infection and active malignancy were the 3 most common reasons that justified not proceeding with a D-dimer assay.

Our proposed criteria for not pursuing antecedent D-dimer testing were based on published literature. Age >80, CRP >110, CKD stage 4 and exacerbations of moderate or severe COPD were selected as reasons.

D-dimer increases with age in healthy volunteers.[7] In two separate studies, in cohorts of patients >80yrs who presented to the emergency department with clinical suspicion of VTE, 0 per cent[8] and 4.8 per cent[9] of patients had a negative D-Dimer. The mean D-dimer in the former study that had no negative values was 7.22mg/L in cases that did not have a PE (personal correspondence), thus age >80 was selected.

There is a paucity of published data on severity of illness and concurrent elevations in D-dimer. One case series report the receiver operator characteristic curve for serum CRP at the time of diagnosis of community acquired pneumonia for discrimination between mild and severe was 110mg/L at its optimum cut-off.[10] The corresponding receiver operating characteristic optimum cut-off value for D-dimer for the same outcome was 0.60mg/L, 20 per cent higher than the reference cut-off, thus CRP 110mg/L was

chosen.

D-dimer values rise 5 per cent for every 10mL/min/1.73m$^{-2}$ decline in eGFR,[11] with a statistically significant difference between healthy controls and CKD stage 4.[12] During the investigation for PE (with no PE on confirmed by CTPA), no patient with CKD stage 4 had a normal D-dimer, and 93.2 per cent of patients with CKD stage 3 had a positive D-dimer with no evidence of PE on CTPA,[13] therefore CKD stage 4 was chosen.

Finally, D-dimer correlates with the severity of COPD,[14] no patients with moderate or severe COPD exacerbations had negative D-dimer when measured within 48 hours of presentation.[15] Accordingly, this was also chosen as a metric for this study.

D-dimer increases with heart failure and heart failure exacerbations,[16] however there is conflicting evidence on the magnitude of this effect; a significant portion of cases overlap into the normal range.[17,18] D-dimer increases with both cirrhosis and ascites, with a statistically significant association between Child Pugh grading and D-dimer value,[19,20] however the IQR of D-dimer crosses into the normal range in these conditions.[21,22] Cirrhotic patients with and without ascites have statistically different D-dimer values independent of Child Pugh grade, however a significant portion crossover into the normal reference range. Accordingly, decompensated heart failure and cirrhosis were not considered justifiable reasons to avoid a D-dimer in this study.

Three hundred and eleven of our 348 acute medical patients met at least one of these criteria to not undergo antecedent D-dimer testing. Of the 47 that did not, 17 of these were approaching but did not reach the pre-defined criteria. A further six patients had decompensated cirrhosis or heart failure and two had severe inflammatory bowel disease proven endoscopically and, as mentioned, conflicting data meant that these were premorbid conditions were not considered.

The remaining 19 patients had a variety of other diagnoses which have not studied in relation to D-dimer, including acute kidney injury, rhabdomyolysis, rheumatological conditions, acute haemorrhage and venous ulcers, therefore were not able to be considered.

There were 34 positive D-dimers in our group, and by our criteria, 28 had a premorbid reason for this to be elevated. Of the six others, five were close to our criteria (four in their late 70s, one with stage 3 CKD), and the remainder had acute kidney injury, where D-dimer has not been studied.

There are two published studies evaluating D-dimers in medical inpatients. Yamada et al.[5] performed CUS and a concurrent D-Dimer at a median of 12 days into their admission. There was a 10.6 per cent incidence of DVT. A total of 29.4 per cent of patients had a D-dimer lower than 1.0mg/L but it is not known how many had a D-dimer lower than the accepted reference cut-off of 0.5mg/L.

Matsuo et al.[4] reported on their cohort of bed-bound medical patients and performed D-dimer and CUS between day 6 and 14. Investigations were withdrawn if patients were no longer bed bound. There was a 33.3 per cent incidence of DVT in this series. 9.5 per cent of patients had a D-dimer lower than their threshold of 0.9–1.0mg/L. Similar to previous, it is not known how many had a D-dimer lower than 0.5mg/L. These studies are of interest but do not add value to current acute medical practice. Firstly, assessment for DVT was not done early in the admission, so these studies reported on the development of DVT rather than investigating DVT as a comorbid presenting medical diagnosis, without documentation of the use of VTE prophylaxis. Secondly, a higher threshold cut-off is utilised which is not prospectively validated, and thirdly, mean length of stay is 36.2 days in one of those studies;[5] the second study does not mention length of stay.

## Conclusion and Limitations

This study is the first of its kind to evaluate D-Dimer appropriateness in acute medical inpatients and has a number of strengths. Firstly, the criteria accepted to not pursue a D-Dimer was pre-defined based on clinical acumen and supported as best as possible with published literature. These criteria were binary in nature to mitigate any potential bias, however this could also be perceived as a weakness, where patients approaching the binary criteria in more than one domain are not able to be considered, even though it seems logical that each factor that influences the D-Dimer would be summative.

Secondly, this study considers typical acute medical inpatients that are discharged relatively rapidly which is reflective of tertiary acute medical units and finally, no patient was excluded due to incomplete data collection. There are a number of limitations to this case series. Firstly, the case series is retrospective in nature and is limited to a single tertiary centre. Secondly, this study population was obtained using the imaging database and accordingly there is no data on how many acute medical inpatients underwent a D-dimer test and did not proceed to ultrasound. Another limitation to this study is the lack of

high quality evidence pertaining to conditions that influence the D-dimer. It is plausible that if there were more rigorous literature on this topic, that it may influence the final results somewhat however our results and conclusions are established using the best available evidence which.

This study supports the limited role for antecedent D-Dimer use in acute medical inpatients, due to their comorbid conditions.

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## PEER REVIEW

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## CONFLICTS OF INTEREST

The authors declare that they have no competing interests.


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## ETHICS COMMITTEE APPROVAL

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**Table 1: Clinical reason(s) and cut-offs identified that justified not using a D-dimer assay prior to preceding to compression ultrasonography for the investigation of DVT**

| |
|---|
| Active malignancy |
| Known arterial thrombus |
| Acute coronary syndrome |
| Acute stroke |
| Significant infection/inflammation (CRP > 110 mg/L) |
| CKD stage 4 or worse (eGFR < 30) |
| Age 80 or above |
| PE or DVT already identified |
| Pregnancy/Postpartum |
| Exacerbation of Moderate or Severe COPD |

**Table 2: Reasons identified why patients did not receive antecedent D-dimer testing**

| Reason | Number of patients |
|---|---|
| Age 80 or above | 103 |
| Significant infection/inflammation | 97 |
| Active malignancy | 55 |
| CKD stage 4 or worse | 34 |
| PE or DVT already identified | 26 |
| Known arterial thrombus | 13 |
| Clinical question of collection, not DVT | 8 |
| Exacerbation of Moderate to Severe COPD | 4 |
| Pregnant/Postpartum | 3 |

*Adds up to >100% as cases often had >1 identifiable reason*