Age-Adjusted D-Dimer Cutoff in Ruling Out Pulmonary Embolism among Saudi Arabians in Riyadh Province

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Abstract
Objective. The study aimed to investigate the effectiveness of an age-adjusted D-dimer (AADD) cutoff in ruling out pulmonary embolism (PE) among the Saudi population, addressing the lack of data on AADD utility in this demographic.

Methods. This single-centre retrospective cohort study conducted at Department of Medicine, King Abdulaziz Medical City in Riyadh, Saudi Arabia, between 2010 and 2018 analysed the data from patients suspected of PE who underwent computed tomography pulmonary angiography (CTPA). Age-adjusted D-dimer (AADD) levels were calculated for patients over 50 years of age [(age × 10) µg/L], and AADD cutoffs were compared for diagnostic accuracy.

Results. Among 277 subjects meeting inclusion criteria, a significant association between D-dimer levels and PE presence was observed. The AADD criteria showed a specificity of 94.7% and a sensitivity of 25%, with a Youden index of 0.2. The high negative predictive value of 90.62% supported the use of AADD in confirming the absence of PE in patients.

Conclusions. Based on the study findings, the AADD cutoff [(age × 10) µg/L] can be efficiently and safely used as an exclusionary tool for patients over 50 years of age suspected of having PE. This study supports the clinical utility of AADD, particularly in older Saudi patient populations.

Keywords
Age-Adjusted D-Dimer; Computed Tomography; Pulmonary Embolism; Saudi Arabia; Clinical Prediction

Introduction
The incidence of pulmonary embolism (PE) is approximately 60-120 cases per 100,000 people per year [1, 2]. However, the prevalence of PE in the general population of Saudi Arabia is unknown. Reports from tertiary centres suggest a variable incidence of PE, ranging from 1.7-33.8/100 patients, across different regions of Saudi Arabia [3–7]. In clinical practice, computed tomography pulmonary angiography (CTPA) is the most commonly used diagnostic investigation to ascertain PE in suspected patients, with an estimated sensitivity of approximately 83% and a specificity of 96% [8]. However, CTPA may have a risk of side effects due to contrast media, and it is both expensive and not readily available [9]. A review has reported that levels of D-dimer, a fibrin degradation product, are highly sensitive in detecting PE, particularly if combined with a pre-test probability (PTP) [10]. Although the rising incidence of PE and the relatively lower specificity of D-dimer measurements, compared to their sensitivity, result in more patients being subjected to further diagnostic tests. Despite this, a meta-analysis has revealed that the D-dimer level is helpful in the exclusion of PE without additional imaging testing [11]. In general, among adults, a D-dimer level < 500 µg/L, in conjunction with a low PTP, can exclude PE in about one-third of outpatients; however, it is to be noted that the D-dimer level may get elevated with age. Age-related elevated levels of D-dimer (a false-positive result) are often attributed to factors such as race and comorbidities, including diabetes mellitus (DM), cardiovascular...
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Materials and Methods

Study Design
This retrospective descriptive hospital-based study was conducted at the Department of Medicine, King Abdulaziz Medical City in Riyadh, Saudi Arabia, using electronic case files and radiology database of all patients who underwent CTPA for suspected PE between 2010 and the end of 2018 (data after 2018 could not be retrieved due to administrative reasons).

Study Population and Eligibility Criteria
All medical records of subjects who underwent CTPA for suspected PE at the emergency department were reviewed.

Inclusion criteria comprised individuals aged 50 years or older who underwent CTPA for suspected PE. Exclusion criteria were no D-dimer testing or incomplete notes. Out of 661 subjects screened, 277 met the study selection criteria and were included in the analysis.

Data Collection
The reviewed information encompassed details such as age, gender, comorbidities (e.g., DM, hypertension (HT), heart failure (HF), CVD, chronic obstructive pulmonary disease (COPD), smoking, obstructive sleep apnea (OSA), cancer), presenting symptoms (e.g., chest pain, syncope, dyspnea, cough, hemoptysis), lower limb pain, swelling, immobilization or casting in the lower limb within the last four weeks, and a history of surgery within the last four weeks. Additionally, blood investigation results were examined, including D-dimer levels, platelet count, and creatinine levels.

Pulmonary Embolism and D-Dimer Interpretation Strategy
The AADD value was calculated based on the method outlined in the previous report [16]. A 10 µ g/l increase per patient year was determined to be an appropriate new D-dimer coefficient. Thus, patients aged 50 years or older had their age multiplied by 10 to establish the AADD cutoff value. Acute PE refers to the obstruction of the pulmonary artery or one of its branches by material (e.g., thrombus, tumour, air, or fat) originating elsewhere in the body. The diagnosis was based on a CT angiogram report from the radiology department confirming thrombus as the main cause of the obstruction.

Statistical Analysis
IBM SPSS version 26 was used for statistical analysis. Presenting symptoms, comorbidities, and CTPA results were presented as percentages, while age and blood investigation results, including D-dimer levels, platelet count, and serum creatinine levels, were reported as mean values with standard deviations.

A 2x2 table was constructed based on whether individual patients’ D-dimer results were categorized as ≥ AADD level or < AADD level. The data were analysed using the Chi-square test with a 95% confidence interval (CI) with phi-coefficient (for measures of association). In addition, the characteristics of the performance assessment were reported with a 95% CI. The statistical significance was set at a p-value < 0.05.
Results

Most patients were females and presented with chest pain and dyspnea. Other common symptoms included syncope, cough, limb swelling, and a history of surgery within the last four weeks (Table 1).

Table 1. General overview of patients’ profile.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>70.96±12.82</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76</td>
</tr>
<tr>
<td>Female</td>
<td>201</td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>127</td>
</tr>
<tr>
<td>Pleuritic</td>
<td>54</td>
</tr>
<tr>
<td>Non-pleuritic</td>
<td>96</td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>252</td>
</tr>
<tr>
<td>Present</td>
<td>25</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>132</td>
</tr>
<tr>
<td>Present</td>
<td>145</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>227</td>
</tr>
<tr>
<td>Present</td>
<td>50</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>272</td>
</tr>
<tr>
<td>Present</td>
<td>5</td>
</tr>
<tr>
<td>Limb pain</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>262</td>
</tr>
<tr>
<td>Present</td>
<td>15</td>
</tr>
<tr>
<td>Limb swelling</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>252</td>
</tr>
<tr>
<td>Present</td>
<td>25</td>
</tr>
<tr>
<td>Four-week immobilisation</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>260</td>
</tr>
<tr>
<td>Present</td>
<td>17</td>
</tr>
<tr>
<td>Surgery within last four weeks</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>257</td>
</tr>
<tr>
<td>Present</td>
<td>20</td>
</tr>
</tbody>
</table>

The mean age of the selected subjects was 70.9 years, and the observed mean D-dimer level was 245.9 µg/L (Table 1, 2).

Table 2. Other clinical characteristics of study participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>303.04</td>
<td>112.93</td>
</tr>
<tr>
<td>Creatinine level</td>
<td>81.78</td>
<td>93.64</td>
</tr>
<tr>
<td>Observed D-dimer level</td>
<td>245.96</td>
<td>292.56</td>
</tr>
</tbody>
</table>

The most common comorbidities included DM, HT, HF, and CVD (Table 3).

A Chi-square test of independence revealed a significant association between D-dimer levels and PE presence ($p < 0.001$) (Table 4).

Out of 277 participants, 21 (7.5%) met the AADD criteria, with 8 (2.8%) showing PE on CTPA. Conversely, of the 256 patients not meeting the AADD criteria, 24 (8.6%) had PE on CTPA (Fig. 1).

Overall, the AADD criteria revealed a specificity of 94.7% (95% CI 91.1%-97.1%) and a sensitivity of 25% (95% CI 11.4%-43.4%) (Table 5).

Discussion

CTPA generally provides a quick and accurate PE diagnosis, which is crucial for timely treatment and reducing
associated risks. However, physicians face challenges in deciding on PE testing due to legal, administrative, and cognitive biases. Divergent opinions, variable D-dimer levels, and a preference for CT scans further complicate the diagnostic process. Using D-dimer testing to rule out PE in patients with a low clinical likelihood can streamline decision-making, reduce unnecessary CT scans, and address resource constraints, thereby improving patient management and outcomes [39]. Additionally, addressing mental health issues such as anxiety, depression, and post-traumatic stress disorder in these patients is vital for comprehensive care [40].

This retrospective study attempted to assess the efficacy of AADD using the D-dimer assay, which increases by 10 µg/L per patient year after the age of 50 years. Most published studies reported using a conventional cutoff of 500 ng/ml [11]. In this study, AADD significantly predicted the presence of PE. The findings revealed that low levels of D-dimer below the AADD cutoff significantly correlated with PE absence. Specifically, 232 out of 245 patients in this study did not have PE according to CTPA results.

In this study, 8 out of 32 patients with PE met the AADD criteria. Further analysis revealed a sensitivity of 25% and a specificity of 94.7%. These findings suggest that the AADD cutoff may effectively exclude a significant proportion of PE patients within the Saudi population. Previously, a study from Saudi Arabia revealed that age-adjusted D-dimer tests demonstrated strong concordance in predicting PE, with high sensitivity but low specificity [32]. This finding underscores the importance of using probability measures before proceeding with more expensive investigations such as CTPA. In Saudi Arabia, it is not uncommon for tertiary care centers offering specialized services to underutilize clinical prediction rules [33]. There is a pressing need to raise awareness among healthcare providers to alleviate the burden on patients and healthcare resources, especially given the shortage of specialized human resources.

In contrast to previous reports, our findings revealed a low sensitivity but high specificity of AADD, accompanied by a low Youden index [2, 26]. This indicates that while AADD effectively identifies individuals without PE (resulting in few false positives), it may not effectively capture all actual cases of the condition, as evidenced by its high rate of false negatives. The low Youden index suggests that AADD may not be considered a standalone diagnostic tool. Therefore, it could be used as a rule-out diagnostic tool rather than a definitive diagnostic tool. The high NPV of 90.62% supports its use in confirming PE absence in patients, thereby reducing the need for more invasive tests when the result is negative. On the other hand, due to its low sensitivity, a positive result alone is insufficient to diagnose PE, necessitating further diagnostic imaging or tests to confirm the presence of the condition. The reasons for this discrepancy are not straightforward; however, several factors may have contributed to this observation. The initial report from Saudi Arabia suggested a link between elevated D-dimer levels and increasing age among Saudis [34], a finding subsequently supported by other studies [32, 35]. Thus far, only one report from Saudi Arabia has indicated a low sensitivity of D-dimer in predicting PE in suspected patients; however, D-dimer levels were not age-adjusted [32]. Another possible reason could be that most patients with PE exhibited segmental involvement in their CTPA results. It has been reported that sensitivity may decrease when PE is limited to segmental involvement [36]. Additionally, the sample size of this study was relatively smaller compared to most reports, resulting in a lower prevalence of PE. A significant proportion of participants had DM and HT. However, contrary to previous reports suggesting that these comorbidities may elevate D-dimer levels [36, 41, 42], no such association was found in the data analysis of this study.

In addition, the incidence of thrombotic phenomena varies across different parts of Saudi Arabia, influenced by altitude [28]. Moreover, D-dimer levels among the Saudi population tend to fall at the lower end of the reference range compared to Western population [30]. Regarding the higher specificity observed compared to previous reports [26], there is a possibility that specificity increases with advancing age [43]; although no study has yet confirmed this elevated level. This finding suggests that AADD may effectively exclude true positive cases of PE in suspected patients.

In this study, demographic and clinical characteristics were similar to those reported previously [32, 34]. A proportion of patients had comorbid DM, consistent with previous reports from Saudi Arabia [4, 6], where DM and HT alongside obesity were recognized risk factors in this population [33, 34]; however, no such associations were identified in this study.

**Limitations**

Data were collected retrospectively from patients undergoing CTPA at a single tertiary care center, and geographic factors could potentially influence the findings. To confirm these results, a prospective multicenter study with a larger sample size is needed.

**Conclusions**

Based on the study findings, the AADD cutoff [(age × 10) µg/L] can be efficiently and safely utilised as an exclusionary tool for patients over 50 years of age suspected of having PE (Se=25%, Sp=94.69%, NPV=90.62%, and PPV=38.10%). This study underscores the clinical utility of AADD, particularly in older Saudi patient populations.

**Ethical Statement**

This research was conducted in accordance with ethical standards outlined in the Helsinki Declaration and adhered to ethical guidelines. Approval was obtained from the institutional Ethics Committee (reference number - RC17/337/R).
Informed Consent
Not applicable due to retrospective descriptive nature of study.

Data Availability
The data supporting this study findings are available from the corresponding author upon reasonable request.

Conflict of Interest
The authors declare that they have no conflicts of interest.

Financial Disclosure
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References


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