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Original Article

Internal Medicine Section

Diagnostic Performance of D-Dimer Compared to Wells and Geneva Scores for Pulmonary Embolism in COVID-19: A Retrospective Cohort Study

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ABSTRACT

Introduction: Classical clinical prediction rules (Wells and Geneva) are widely used to assess the risk of Pulmonary Embolism (PE). Still, their performance in Coronavirus Disease 2019 (COVID-19) is uncertain, given frequent D-Dimer (DD) elevations unrelated to thrombosis.

Aim: To compare the diagnostic performance of an optimised DD cut-off against Wells and Geneva scores in Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) confirmed COVID-19 patients with suspected PE.

Materials and Methods: A retrospective, single-centre cohort study was conducted at Department of Internal Medicine, Consorci Sanitari de Terrassa, Barcelona, Spain, from Consorci Sanitari de Terrassa (Barcelona, Spain) from January 2021 to June 2021. Adult COVID-19 patients undergoing Computed Tomography Pulmonary Angiography (CTPA) for suspected PE were analysed. Receiver Operating Characteristic (ROC) analysis was used to assess DD, Wells, and Geneva; the optimal DD threshold was identified by Youden's index. Group comparisons used t-test or Mann-Whitney U for continuous variables and Chi-square or Fisher's-exact test for categorical variables; p-value <0.05 was considered significant.

Results: CTPA was performed in 586 patients, of whom 148 had confirmed COVID-19 infection. PE was diagnosed in 13.5% (20/148) of cases. Patients with PE had significantly higher DD levels than those without PE (p-value <0.05). A DD threshold of 3126 ng/mL yielded 80% sensitivity and 68.5% specificity, potentially avoiding 87 CTPAs while missing 4 PE diagnoses. In comparison, the Wells score showed poor performance {Area Under Curve (AUC) 0.60, 95% Confidence Interval (CI) 0.48-0.72; sensitivity 55%, specificity 56%}, whereas the revised Geneva score was even less accurate (AUC 0.41, 95% CI 0.26-0.55; sensitivity 45%, specificity 55%).

Conclusion: In the present cohort of COVID-19 patients with suspected PE, an optimised DD cut-off demonstrated superior discriminatory performance compared to conventional clinical prediction rules. Therefore, in COVID-19 settings with suspected PE, a DD threshold of approximately 3,126 ng/mL may help reduce unnecessary Computed Tomography (CT) pulmonary angiographies when interpreted in conjunction with clinical probability and physician judgment.

Keywords: Coagulopathy, Coronavirus disease 2019, Emergency service, Fibrin, Thromboembolism, Tomography

INTRODUCTION

Pulmonary Thromboembolism (PE) has been described as a complication in COVID-19 infection [1]. The infection, even with adequate anticoagulation, seems to provide a prothrombotic state for the development of thrombotic events in relation to local vascular damage [2]. In studies focused on patients with a clinical suspicion of PE, the reported prevalence in COVID-19 settings shows substantial variation. Meta-analyses have described pooled PE prevalences around 7.65% overall, with higher rates in ICU cohorts (~12%) [3], while single-centre Intensive Care Unit (ICU) series have reported cumulative incidences around 20% by day 15 [4]. These estimates reflect patients who underwent CTPA because of clinical suspicion, rather than all COVID-19 cases.

The DD is an acute-phase reactant used in the diagnostic algorithms of PE; below the conventional cut-off of 500 ng/mL, the likelihood of PE is usually excluded with high certainty [5]. The original Wells score [6] and revised Geneva score [7] are also commonly applied in PE diagnostic pathways, as recommended by European guidelines [8].

However, classical prediction rules such as the original Wells score and the revised Geneva score were developed and validated in non COVID populations. COVID-19 is associated with endothelial dysfunction, systemic inflammation, and a hypercoagulable state, frequently leading to markedly elevated DD levels even without thromboembolic events [9]. This high baseline elevation of DD may compromise the specificity of the biomarker and challenge the applicability of conventional diagnostic algorithms in this population. This discrepancy has led clinicians to question whether these tools retain their diagnostic accuracy in the setting of COVID-19. Authors have recommended higher DD thresholds [10] as well as adjustments to diagnostic strategies specifically for COVID-19. Several studies have addressed the diagnostic challenge of PE in COVID-19 patients, particularly regarding DD thresholds. Ventura-Díaz S et al., proposed using a higher DD threshold for predicting PE in COVID-19 patients, recognising that these patients typically present elevated DD levels due to the inflammatory response of the disease itself, not solely from thrombosis, which causes the conventional threshold (500 ng/mL) to generate numerous false positives and unnecessary imaging studies [11]. Similarly, Revel MP et al., evaluated what level of DDs could safely exclude PE in COVID-19 patients presenting to the emergency department, aiming to determine an optimal DD threshold specific for the COVID-19 population [12]. While the YEARS study by Van der Hulle T et al., was conducted before the pandemic and is not COVID-19 specific, it presents a simplified diagnostic algorithm for suspected PE that

combines clinical criteria with adjusted DD levels, an approach that has been subsequently evaluated and adapted for use in COVID-19 patients [13]. These studies collectively highlight the need to adjust diagnostic strategies in COVID-19 patients to avoid unnecessary testing while maintaining diagnostic safety.

Given these limitations, traditional diagnostic tools for COVID-19 remain controversial. The clinical challenge is two-fold: avoiding missed PE diagnoses, which carry high morbidity and mortality, while also preventing unnecessary CTPA examinations that expose patients to radiation and contrast and overburden radiology services during pandemic surges [14,15]. Therefore, the novelty of the present study lies in assessing whether an optimised DD cut-off could provide a better balance between sensitivity and specificity than Wells and Geneva scores, offering a practical alternative for clinicians managing suspected PE in this complex patient population. Hence, the study aimed to evaluate whether an optimised DD cut-off could outperform the original Wells score and the revised Geneva score in diagnosing PE in COVID-19 patients with a high clinical suspicion of PE. The primary objective was to compare the diagnostic performance of this optimised DD threshold against both clinical prediction rules. And the secondary objectives were to estimate the Area Under the Receiver Operating Characteristics (ROC) curve (AUC) for DD, Wells, and Geneva scores; to quantify the potential impact of the DD threshold on the avoiding unnecessary CTPA; and to describe the prevalence of PE confirmed by CTPA.

MATERIALS AND METHODS

This retrospective single centre cohort study was conducted at the Department of Internal Medicine, Consorci Sanitari de Terrassa, Barcelona, Spain, from January 2021 to June 2021. The protocol was approved by the Consorci Sanitari de Terrassa Research Ethics Committee (approval number: 05-22-101-041). Because of the retrospective design, informed consent was waived. All data were anonymised, and each patient was identified by a unique alphanumeric code, in compliance with relevant guidelines and regulations. The 6-month period corresponded to the peak COVID-19 waves in the Spanish region during which systematic CTPA protocols were in place, ensuring uniform diagnostic and data collection criteria.

Inclusion criteria: Adult patients (≥18 years) with RT-PCR-confirmed COVID-19 infection who underwent CTPA specifically for clinical suspicion of PE during the study period.

Exclusion criteria:

1. Patients without Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) confirmation by RT-PCR.
2. CTPA was performed for indications other than suspected PE.
3. Incomplete medical records prevent the calculation of Wells or revised Geneva scores.

Study Procedure

Patients were classified as PE-positive based on CTPA findings. Wells and revised Geneva scores were calculated post-hoc from clinical records. The original Wells score [6] and the revised Geneva score [7], with their standard cut-off points, without altering any official criteria, were used. The revised Geneva score was selected to ensure consistency with local clinical protocols during the study period. At the Institution, non COVID-19 patients with suspected PE typically have their Wells components recorded in the electronic request.

- As per the Original Wells score [6], Patients were categorised as low (<2), moderate (2-6), or high (>6) pretest probability.
- Revised Geneva score [7] ranges from 0 to 25 points: Patients were categorised as low (0-3), intermediate (4-10), or high (≥11) pretest probability.
- DD levels were measured with automated latex-enhanced turbidimetric immunoassays (ACL TOP 500®). A threshold of 500 ng/mL was considered the upper limit of normal for DD [5].

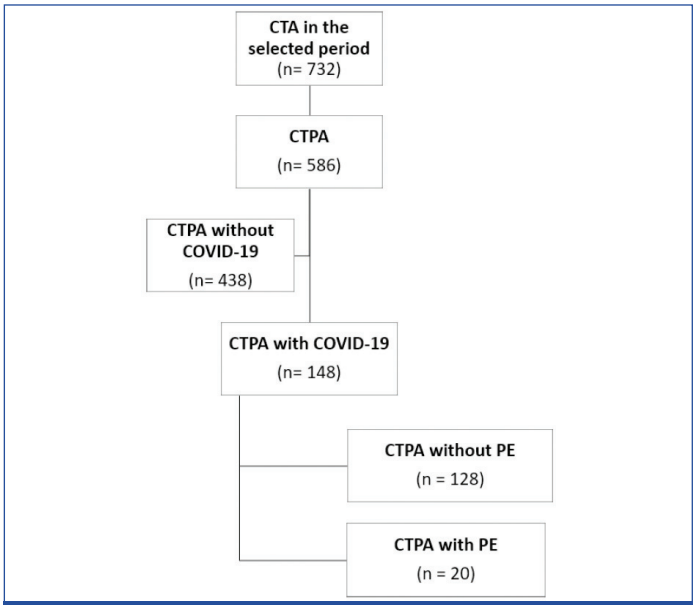
Data were extracted from electronic patient records, including Wells score components, revised Geneva score components, age, cardiovascular risk factors, the ratio of arterial oxygen partial pressure (PaO_2) to fraction of inspired oxygen (FiO_2) (PaO_2/FiO_2) mean, previous anticoagulant therapy, and vaccination status. Patients were divided into two subgroups based on a positive or negative PE finding on CTPA [Table/Fig-1].

STATISTICAL ANALYSIS

All analyses were performed with Statistical Package for Social Sciences (IBM SPSS) version 27.0 (IBM Corp).Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as means with Standard Deviations (SD) or medians with Interquartile Ranges (IQR). Two-tailed tests (t-test or Mann-Whitney for continuous data, Chi-square or Fisher's-exact test for categorical data) were applied, considering p-value <0.05 as statistically significant. Contingency tables were built to assess the diagnostic accuracy of DD using CTPA as the gold standard. The discriminative ability of DD was determined by ROC curve analysis. The optimal DD cut-off was identified by maximising Youden's index (sensitivity + specificity - 1). Sensitivity, specificity, and negative predictive value were calculated at that threshold.

RESULTS

During the study period, a total of 732 Contrast-enhanced angiographic CT (CECT) examinations were performed at the study Institution. Of these, 586 were CTPA performed due to clinical suspicion of PE. As part of Institutional pandemic protocols, all patients undergoing CTPA also underwent RT-PCR testing for SARS-CoV-2 during the same clinical episode. Among these 586, 148 had confirmed SARS-CoV-2 infection and were included in the study, while the remaining 438 had negative RT-PCR results and were excluded [Table/Fig-1].



[Table/Fig-1]: Flowchart of the study participants.
COVID-19: Coronavirus disease 2019; CTPA: Computed tomography pulmonary angiography.

The mean age of the 148 patients was 65 ±16, and 82 (55.5%) were males. Of these, 132 (89.2%) had pneumonia. PE was confirmed in 20 (13.5%) patients, among those with clinical suspicion, rather than in the overall COVID-19 population.

The mean PaO_2/FiO_2 was 330.8 ±132.7 overall, with no significant differences between patients with PE and those without PE (p-value=0.197).

Similarly, pneumonia distribution did not differ between groups (p-value=0.698). Among them, 6 patients (4.1%) had a previous thrombosis, 10 (6.8%) were on anticoagulant therapy, and 26 (17.6%) had been vaccinated. None of these variables differed significantly between groups [Table/Fig-2].

The DD levels were elevated (>500 ng/mL) in 135 of 148 patients (91.2%). The median DD level was 2231 ng/mL (IQR: 1079-4426). Patients with PE had significantly higher DD levels than those without PE (p-value <0.05) [Table/Fig-2].

Characteristics	All (n=148) n (%)	No PE (n=128) n (%)	PE (n=20) n (%)	p-value
Male	82 (55.4%)	68 (53.1)	14 (70)	0.226
Age (years) (mean±SD)	65±16	65±16	67±15	0.598
PAFi (mean± SD)	330.8±132.7	336.9±125.2	294.3±170.9	0.197
Hypertension	83 (56.1)	72 (56.3)	11 (55)	1.000
Diabetes mellitus	40 (27)	32 (25)	8 (40)	0.180
Dyslipidemia	60 (40.5)	48 (37.5)	12 (60)	0.085
Cancer	16 (10.8)	15 (11.7)	1 (5)	0.698
Pneumonia	132 (89.2)	113 (88.3)	19 (95)	0.698
Previous thrombosis	6 (4.1)	5 (3.9)	1 (5)	0.588
Vaccine	26 (17.6)	23 (18)	3 (15)	1.000
Anticoagulant therapy	10 (6.8)	10 (7.8)	0 (0)	0.359
D-Dimer (DD) (ng/mL),	2231	1786	4380.5	<0.001
Median (IQR)	(1079-4426)	(997-3875)	(3317.5-10191.5)	
Wells score (mean±SD)	3.55±1.28	3.49±1.33	3.92 ±0.86	0.163
Geneva score (mean±SD)	4.09±2.45	4.21±2.43	3.35±2.51	0.145

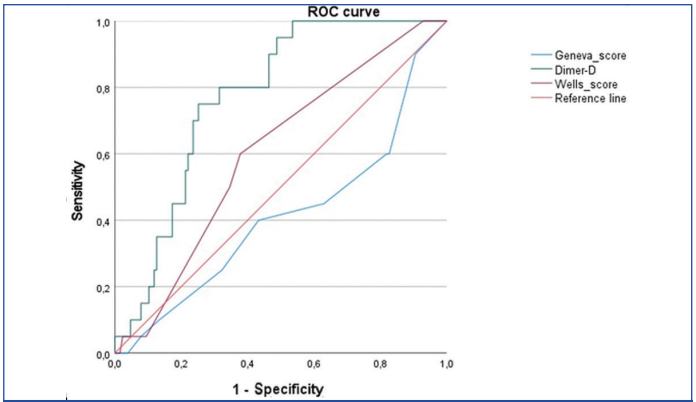
[Table/Fig-2]: Baseline characteristics of the study population of coronavirus disease 2019 patients who underwent CTPA.
PE: Pulmonary embolism; SD: Standard deviation; IQR: Interquartile range (Q1-Q3). Continuous variables are expressed as mean ±SD or median (IQR). PAFi, Wells score y Geneva score were compared using Student's t-test, D-dimer using Mann–Whitney U test. Categorical variables are presented as n (%) and compared with chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant

A DD value of 3126 ng/mL yielded 80% sensitivity and 68.5% specificity, providing the best trade-off according to Youden's index. If that threshold had been used in clinical practice, 87 CTPAs could have been avoided, at the cost of missed 4 PE diagnoses [Table/Fig-3].

D_dimer threshold (ng/mL)	Sensitivity (%)	Specificity (%)	NPV (%)	Accuracy (%)	CTPA Correctly avoid	Missed PE diagnosis
1500	100	42.5 (34 - 51.1)	100	50.3	54	0
2000	90 (100 – 76.8)	52.7 (44 - 61.4)	97.1	57.8	67	2
3126	80 (62.4 – 97.5)	68.5 (76.5 - 60.4)	95.6	70	87	4
5000	45 (23.2 – 66.8)	81.1 (74.3 - 88)	90.3	76	103	11

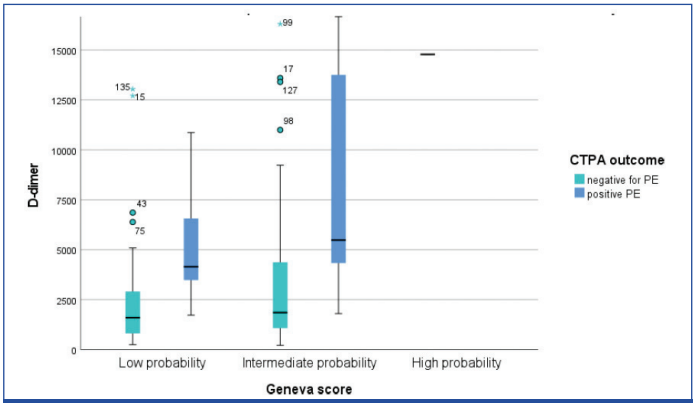
[Table/Fig-3]: Sensitivity, specificity, Negative Predictive Value (NPV), accuracy of each D-Dimer (DD) threshold and the corresponding number of CTPA correctly avoided and missed diagnosis of Pulmonary Embolism (PE).

In the ROC analysis, DD showed an AUC of 0.77 (95% CI 0.68-0.85), indicating moderate to good diagnostic performance. The Wells score had an AUC of 0.60 (95% CI 0.48-0.72), considered moderate to low, while the revised Geneva score had an AUC of 0.41 (95% CI 0.26-0.55), considered low [Table/Fig-4].

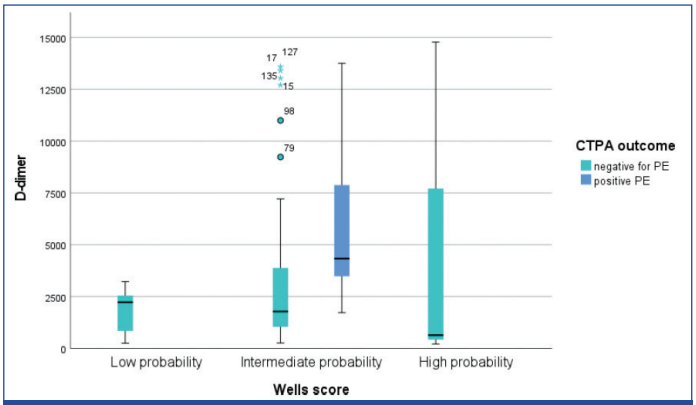


[Table/Fig-4]: Receiver Operating Characteristics (ROC) curve illustrating the diagnostic performance of various prediction rules to assess the risk of Pulmonary Embolism (PE) in COVID-19 patients suspected of having PE.

The distribution of DD levels according to Wells and revised Geneva categories is displayed in [Table/Fig-5,6]. According to Wells categories, 1/20 (5%) of PE patients had high probability, 19/20 (95%) moderate, and 0/20 (0%) low. For the revised Geneva score, 9/20 (45%) were classified as intermediate probability and 11/20 (55%) as low, with 0/20 (0%) in the high-probability group.



[Table/Fig-5]: Distribution of D-Dimer (DD) values in patients with COVID-19, considering the Geneva score for Pulmonary Embolism (PE).



[Table/Fig-6]: Distribution of D-Dimer (DD) values in patients with COVID-19, considering Wells score for Pulmonary Embolism (PE).

DISCUSSION

The present study observed that most patients (91%) had elevated DD levels, largely explained by the fact that only those with signs or symptoms suggestive of PE were included. This high prevalence of elevated DD is consistent with the hypercoagulable state characteristic of COVID-19 [15]. Similarly, Engels SYH et al., reported that elevated DD levels were widespread in their cohort of hospitalised COVID-19 patients, with median values significantly higher in those with PE [16]. Brem L et al., also documented this phenomenon, observing that DD levels were significantly elevated in COVID-19 patients even in the absence of PE, with median values of 2980 ng/mL in patients without PE compared to 14680 ng/mL in those with PE [17].

The 3126 ng/mL cut-off was determined by optimising Youden's index in the present cohort, offering both reasonable sensitivity and specificity, though with wide confidence intervals due to the relatively small sample size and limited number of PE cases (n=20). This threshold aligns with recent evidence suggesting higher DD cut-offs may improve diagnostic accuracy in COVID-19 patients. Engels SYH et al., identified an optimised cut-off of 750 ng/mL with 100% sensitivity and an AUC of 0.83 to rule out PE in hospitalised COVID-19 patients, demonstrating that adjusted thresholds can maintain high sensitivity [16]. Brem L et al., proposed a threshold of 2600 ng/mL with 90.3% sensitivity and an AUC of 0.773, which is remarkably similar to our findings [17]. Bledsoe JR et al., validated a 2000 ng/mL cut-off in a large multicentre study involving emergency department patients, achieving a negative predictive value of 99.5% in the validation cohort, though with a sensitivity of only 70.5% [18]. These findings collectively support the adaptation of DD thresholds in the COVID-19 context to enhance diagnostic precision and reduce unnecessary imaging.

Interestingly, in the current study the Wells score retained moderate discriminatory power (AUC 0.60), while the Geneva score performed poorly (AUC 0.41). This discrepancy may be partly due to the specific weighting of variables in each score and the unique pathophysiology of COVID-19. For example, tachycardia, hypoxia, and recent hospitalisation are common in COVID-19 patients and may lead to misclassification in these traditional scoring systems. Vielhauer J et al., compared multiple predictive scores including Wells, Geneva, YEARS, and Pulmonary Embolism Graduated D-Dimer (PEGeD) in hospitalised COVID-19 patients and found variable performance across different algorithms, highlighting the challenges of applying traditional risk stratification tools in this population [19]. Rindi LV et al., conducted a systematic review demonstrating that conventional PE prediction scores have reduced accuracy in COVID-19 populations, likely due to atypical presentations and symptoms that overlap with the infection itself [20].

In the present study cohort, the mean revised Geneva score was unexpectedly lower in PE patients than in non PE patients. This counterintuitive finding likely reflects the small sample size and the absence of high-probability cases, as well as the objective structure of the Geneva score, which does not include the subjective clinical judgement variable present in the Wells score and may yield lower scores in COVID-19 patients despite confirmed PE. Rindi LV et al., noted in their systematic review that objective scoring systems may be particularly challenged in COVID-19 populations where clinical features overlap significantly between PE and the underlying infection [20]. This further supports the limited discriminatory power of the score in COVID-19 populations, possibly due to the atypical presentation and overlapping symptoms with the infection itself.

The current study results suggests that in this specific population, COVID-19 patients with clinical suspicion of PE, a higher DD threshold could help reduce unnecessary imaging without significantly compromising sensitivity. However, authors are not suggesting that DD be used as a stand-alone tool, as clinical context and risk stratification remain essential. The evidence from multiple studies supports the need for COVID-specific adaptations of diagnostic thresholds. Engels SYH et al., demonstrated that a 750 ng/mL threshold could reduce unnecessary imaging by 13% compared to the conventional 500 ng/mL cut-off while maintaining 100% sensitivity [16]. Brem L et al., showed that their 2600 ng/mL threshold could avoid 29 CTPAs in their cohort of 84 patients [17]. However, Bledsoe JR et al., cautioned that while higher thresholds achieve high negative predictive values, the associated sensitivities may be too low for standalone clinical application without pretest probability assessment [18]. Future studies with larger sample sizes and prospective designs are warranted to validate our findings and to determine the optimal integration of adjusted DD thresholds with clinical prediction scores in COVID-19 patients.

Although Wells and revised Geneva scores are typically used as categorical tools in clinical settings, they were analysed as continuous variables solely for comparative purposes using ROC analysis. It is acknowledged that this does not reflect their standard clinical application.

Limitation(s)

Systematic lower-extremity ultrasound was not performed in all patients, preventing a reliable assessment of coexisting Deep Venous Thrombosis (DVT); and the potential role of age-adjusted DD thresholds, which are established in non COVID settings were not explored. Subgroup analyses according to COVID-19 severity, time from symptom onset, or prior anticoagulation were not conducted due to the limited sample size, which would have substantially reduced statistical power and increased the risk of type II error. Similarly, while our proposed DD threshold could have reduced the number of CTPAs performed, it would have missed 20% of confirmed PE cases (n = 4); the clinical implications of this trade-off merit careful evaluation in future studies.

Future studies with larger sample sizes and prospective designs are warranted to validate our findings and to assess whether COVID-specific adaptations of these tools could improve diagnostic accuracy.

CONCLUSION(S)

In COVID-19 patients with a high clinical suspicion of PE, DD demonstrated a higher discriminatory capacity than the Wells and Geneva scores, as shown by ROC analysis. A threshold of 3126 ng/mL offered the best trade-off between sensitivity and specificity in this cohort. However, this finding should be considered exploratory and interpreted with caution, given the small sample size and inherent selection bias.

Authors' contributions: MMM, MBP, LR and Catón: A collected the data, MMM and EJ-F: Accomplished data analysis, EJF: Performed imaging processing, MMM and EJF: Drafted the manuscript and made literature review, MMM, and EJF: Reviewed the manuscript. All authors read and approved the final manuscript.

Acknowledgement

Carme Pérez-Ventana contributed to the literature review; Cuadra L. and Cara J.J. have reviewed the final manuscript.

Availability of Data and Materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. All data generated or analysed during this study are included in this published article.

Informed consent statement: IRB at Consorci Sanitari de Terrassa has approved the waiver of patient consent form because of the retrospective nature of this study. Patient confidentiality is maintained at all time in accordance with Consorci Sanitari de Terrassa policies.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 31, 2025
- Manual Googling: Dec 20, 2025
- iThenticate Software: Dec 23, 2025 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. NA

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