



Positive rate and quality assessment of CT pulmonary angiography in sickle cell disease: a case–control study

Ali Hassan¹ · Mohammed Taleb¹ · Wafa Hasan¹ · Fatema Shehab¹ · Reem Maki¹ · Nawal Alhamar¹

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Abstract

Background Pulmonary complications are common in sickle cell disease (SCD) and can mimic pulmonary embolisms (PEs), leading to potential overuse of computed tomography pulmonary angiography (CTPA). Maximizing the quality of CTPA is essential for its diagnostic accuracy. However, little is known about the positive rate and quality of CTPA in SCD.

Methods This retrospective case–control study aimed to determine the positive rate and quality of CTPA studies performed to rule out PE in SCD (HbSS genotype) patients compared to a control group. Logistic regression analysis was used to identify independent factors associated with suboptimal CTPA studies, defined as a mean enhancement of < 210 HU in the pulmonary artery.

Results The study included 480 patients, consisting of 240 SCD patients and 240 controls. The positive rate of PE was 4.0%, with a similar rate in both SCD patients and the control group (4.2% vs. 3.8%, $p = 0.08$). However, SCD patients had significantly lower contrast enhancement of the pulmonary artery than the control group (266.1 ± 90.5 HU vs. 342.2 ± 116.1 HU, $p < 0.01$). Notably, 25.4% of SCD patients had suboptimal scans. The logistic regression model demonstrated that SCD was significantly associated with suboptimal pulmonary arterial contrast enhancement compared to the control group (OR = 4.4; 95% CI: 2.4–8.3).

Conclusions This study revealed a relatively low positive rate of CTPA in both SCD patients and the control group. However, SCD was significantly associated with suboptimal image quality due to inadequate contrast enhancement of the pulmonary artery. Further research is needed to identify measures that can enhance the quality of CTPA studies in SCD patients and to establish a specific imaging protocol for this patient population.

Keywords Computed tomography · Positive rate · Pulmonary embolism · Quality · Sickle cell disease

Background

Pulmonary embolism (PE) is a common and potentially life-threatening medical emergency that requires prompt diagnosis and management to minimize associated morbidity and mortality [1]. However, due to its nonspecific clinical presentation, the diagnosis of PE can be challenging and requires a high level of suspicion to pursue an appropriate diagnostic evaluation. Computed tomography pulmonary angiography (CTPA) remains the preferred first-line imaging investigation for evaluating PE due to its high sensitivity and widespread availability [2]. However, concerns have been raised

about the overuse of CTPA, which can lead to unnecessary radiation exposure and reactions to contrast media [3, 4]. The positive rate of CTPA is often used as an indicator of appropriate utilization, with the Royal College of Radiologists recommending a positive rate greater than 15.4% [5].

Sickle cell disease (SCD) is an inherited monogenic hematologic disorder with a wide spectrum of complications affecting various organ systems. Cardiopulmonary complications are common and are the leading cause of mortality in SCD [6]. The clinical features of these complications can be indistinguishable from those of PE. Notably, up to 90% of patients with SCD were found to have abnormal pulmonary function tests that could be related to underlying asthma, pulmonary hypertension, pulmonary fibrosis, or pulmonary hemosiderosis [7]. Another challenge is the constant elevation of D-dimer levels in SCD, which limits the use of D-dimer-based diagnostic algorithms [8]. Patients with SCD

✉ Ali Hassan
alihy8@gmail.com

¹ Department of Radiology, Salmaniya Medical Complex, Manama, Bahrain

are also at increased risk for thromboembolic events due to their hypercoagulable state [9]. In particular, the mortality rate from PE in SCD is 5%, making it the second most common pulmonary-related cause of death after pneumonia [10]. As a result, distinguishing PE from other pulmonary conditions can be challenging, and the overuse of CTPA in SCD might be expected, considering that the mortality rate of missed PE can be as high as 30% [11]. However, this issue has not been adequately researched, as only a few studies have examined the positive rate of CTPA for PE in SCD [12, 13]. For instance, Bates et al. [13] found no significant differences in the positive rate of CTPA between patients with SCD and those without SCD. However, this study only focused on patients in the emergency department and included a small sample size of 78 individuals with SCD.

Accurate diagnosis of PE relies on the quality of the CTPA study. Adequate contrast opacification of the pulmonary vasculature is an essential factor impacting diagnostic performance, with the Royal College of Radiologists recommending a mean contrast enhancement greater than 210 Hounsfield units (HU) in the pulmonary artery [14]. However, limited studies have evaluated the quality of CTPA in SCD. For example, a retrospective study by Jensen et al. [15] showed that SCD patients had lower contrast opacification of the pulmonary artery and discussed several modifications to the imaging protocol to enhance scan quality. Nonetheless, some of these modifications, such as increasing contrast volume, can lead to potential adverse effects, such as contrast-induced nephropathy. It may be impractical to incorporate such modifications solely based on the findings of a single study involving only 35 patients with SCD. Additionally, Swift et al. [12] reported contradictory findings, indicating that the image quality of CTPA in SCD was similar to, if not better than, that in the control group.

In the Kingdom of Bahrain, the prevalence of the sickle cell trait was 11%, and the prevalence of SCD was 2.1% according to neonatal screening data in 1985 [16]. Despite extensive efforts in premarital screening and counseling, a more recent study in 2011 indicated that the prevalence of SCD among school students was almost 1.0% [17]. Most previous studies on CTPA in SCD suffered from small sample sizes. Therefore, the present study aims to expand our knowledge of the positive rate and quality of CTPA in SCD in the Kingdom of Bahrain, where the disease is relatively prevalent.

Methods

Study design and settings

After obtaining approval from the ethics committee, a retrospective case–control study was conducted to investigate the

prevalence of PE and evaluate the quality of CTPA studies in terms of contrast opacification of the pulmonary arterial vasculature in patients with SCD compared to a control group of patients without SCD. The study was conducted at the Salmaniya Medical Complex, the largest tertiary hospital in the Kingdom of Bahrain, with a capacity of 1200 beds and 1300 daily visits to the emergency department.

Patient selection

The study enrolled all patients with SCD (HbSS genotype) who underwent CTPA for suspected PE and presented to the hospital between January 1, 2018, and December 31, 2021. Both hospitalized patients and outpatients were included, while patients who were pregnant or under the age of 18 were excluded. Age-matched patients without SCD who underwent CTPA during the same period were randomly selected as a control group.

Data collection

A structured data collection form was developed to extract clinical, laboratory, and radiological information from electronic health records. The clinical data collected included age, sex, comorbidities, and SCD status. The laboratory data collected included hemoglobin (g/dL) and D-dimer ($\mu\text{g/mL}$) levels. The radiological data collected included the presence of PE, mean contrast opacification of the pulmonary artery, and the main pulmonary artery diameter. The data were collected by coinvestigators who were trained and closely supervised by the principal investigator.

The Charlson Comorbidity Index, a validated tool that quantifies the burden of comorbid conditions in patients and predicts patient mortality and adverse outcomes [18], was calculated. It includes 17 different components and has a range from 0 to 37, with higher scores indicating a greater burden of disease.

Image interpretation

Contrast opacification was assessed by placing a region of interest over two-thirds of the pulmonary artery at its bifurcation. The CTPA study was considered suboptimal if the mean enhancement of the pulmonary artery was less than 210 HU. The pulmonary arterial vasculature was evaluated for filling defects suggestive of PE. The interpretations were compared to the available radiology reports, all of which were approved by board-certified radiologists, and no discrepancies were found. The diameter of the main pulmonary artery was measured at its bifurcation.

Imaging technique

CTPA studies were conducted using a dual-source 128-slice scanner (Siemens, Erlangen, Germany). The bolus tracking technique was used, in which sequential axial slices were obtained at the level of the pulmonary artery until the 100 HU threshold was reached. Multiplanar reconstructions were obtained in the sagittal and coronal planes. The scanning parameters are summarized in Table 1.

Statistical analysis

The data were collected and organized using Microsoft Excel 2021 (Microsoft, Redmond, WA, USA). After ensuring completeness and consistency, the data were analyzed using IBM SPSS for Windows, version 26 (IBM Corp., Armonk, NY, USA). Figures were used to provide an illustrative summary of the data. Categorical variables, presented as percentages and frequency distributions, were compared using the chi-squared test or Fisher's exact test. The Kolmogorov–Smirnov and Shapiro–Wilk tests determine that the continuous variables were not normally distributed. Hence, continuous variables, presented as medians and interquartile ranges (IQR), were compared using the Mann–Whitney *U* test. Multivariable binary logistic regression analysis was conducted to identify the independent factors associated with suboptimal quality of CTPA. Candidate variables were selected based on medical literature and bivariate analyses. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using the full model fit, and the results were reported in comparison with the designated reference group. The goodness-of-

Table 1 Scanning parameters of CTPA studies

Parameter	Value
Tube voltage	100 kVp
Tube current	200 mA
Beam collimation	0.6 mm
Rotation time	0.5 s
Pitch	1.2
Scan direction	Craniocaudal
Scan extent	From lung apex to diaphragm
Respiration phase	Inspiration
Contrast volume	60 mL followed by 100 mL saline flush
Infusion rate	5 mL/s
Catheter size	16-gauge

fit of the model was evaluated using the Omnibus and

Hosmer–Lemeshow tests. The significance level was defined as $\alpha = 0.05$.

Results

Patient characteristics

As shown in Table 2, the study enrolled 480 patients, including 240 patients with SCD and a similar number of control patients. There were 250 (52.1%) male and 230 (47.9%) female patients. The median age of the patients was 39.0 years (IQR: 31.0–50.0 years). No significant differences in age, sex, or body mass index were found between the SCD and control groups ($p = 0.88$). Furthermore, the Charlson comorbidity index scores were comparable in both groups ($p = 0.27$). Only 5 (1.0%) patients had a history of venous thromboembolic events.

D-dimer level measurements were performed in half of the patient population (50.8%). The median D-dimer level in patients with SCD was significantly higher than that in the control group (4.9 $\mu\text{g/mL}$ vs. 2.7 $\mu\text{g/mL}$; $p < 0.01$). However, no significant difference was observed in the proportion of patients with elevated D-dimer levels between the SCD and control groups (95.8% vs. 90.5%; $p = 0.11$).

Findings of CTPA studies

Table 3 summarizes the positive rate of CTPA according to age, sex, and SCD. Among the 480 patients, 19 had PE, yielding an overall positive rate of 4.0%. Patients with SCD had a positive rate similar to that of the control group (4.2% vs 3.8%; $p = 0.08$). Additionally, no significant difference was observed in the positive rate based on age and sex ($p > 0.05$). Among the 220 patients with elevated D-dimer levels, 7 (3.2%) had PE. The median diameter of the main pulmonary artery was 27.7 mm. There was a statistically significant difference in the median diameter of the main pulmonary artery between the SCD and control groups (28.3 mm vs. 27.0 mm; $p < 0.01$).

Quality of CTPA studies

In total, 79 (16.5%) patients had suboptimal contrast opacification of the pulmonary artery in CTPA studies (Figs. 1 and 2). The mean contrast opacification of the pulmonary artery was 304.2 ± 110.7 HU. However, patients with SCD had a significantly lower contrast opacification of the pulmonary artery than those in the control group (266.1 ± 90.5 HU vs. 342.2 ± 116.1 HU; $p < 0.01$). This difference is further illustrated in Fig. 3.

Table 2 Patient characteristics

Variable	SCD (<i>n</i> = 240)	Control group (<i>n</i> = 240)	Overall (<i>n</i> = 480)	<i>p</i> value	
Age (years)	39.0 (30.3–50.0)	39.0 (31.0–50.0)	39.0 (31.0–50.0)	0.88	
Male sex	130 (54.2)	120 (50.0)	250 (52.1)	0.36	
Body mass index	27.9 (22.9–32.5)	28.7 (23.5–36.3)	28.4 (23.0–34.4)	0.26	
Charlson Comorbidity Index	0	142 (59.2)	303 (63.1)	0.27	
	1–2	65 (27.1)	77 (32.1)		
	3–4	8 (3.3)	14 (5.8)		
	>4	6 (2.5)	7 (2.9)		
			13 (2.7)		
Comorbidities	Myocardial infarction	1 (0.4)	5 (2.1)	6 (1.3)	0.21
	Stroke	0 (0.0)	2 (0.8)	2 (0.4)	0.50
	Chronic kidney disease	3 (1.3)	5 (2.1)	8 (1.7)	0.72
	Venous thromboembolism	3 (1.3)	2 (0.8)	5 (1.0)	1.00
	Connective tissue disease	3 (1.3)	10 (4.2)	13 (2.7)	0.09
	Malignancy	6 (2.5)	13 (5.4)	19 (4.0)	0.16
	On anticoagulant treatment	10 (4.2)	9 (3.8)	19 (4.0)	1.00
D-Dimer	Not performed	122 (50.8)	114 (47.5)	236 (49.2)	0.47
	Elevated	113 (95.8)	114 (90.5)	227 (93.0)	0.11
	Level (µg/mL)	4.9 (2.0–13.5)	2.7 (0.9–9.3)	3.9 (1.3–12.0)	< 0.01

n, number of CTPA studies; SCD, sickle cell disease

Data are presented as median (interquartile range) or frequency (percentage)

Table 3 Rate of positive CTPA studies according to age, sex, and sickle cell disease

Variables	Categories	Positive scans (<i>n</i> = 19)				<i>p</i> value
		<i>n</i>	(%)	OR	(95% CI)	
Age group (years)	18–35	5	(2.6)	Reference group	0.52	
	36–50	12	(5.1)	2.0		(0.7–5.7)
	51–65	2	(4.8)	1.8		(0.3–9.8)
Sex	Male	13	(5.2)	Reference group	0.15	
	Female	6	(2.6)	0.5		(0.2–1.3)
Charlson Comorbidity Index	0	10	(3.3)	Reference group	0.50	
	1–2	6	(4.2)	1.3		(0.5–3.6)
	3–4	2	(9.1)	2.9		(0.6–14.3)
	>4	1	(7.7)	2.4		(0.3–20.7)
Sickle cell disease	No	9	(3.8)	Reference group	0.82	
	Yes	10	(4.2)	1.1		(0.4–2.4)
D-dimer level	Not Elevated	2	(11.8)	Reference group	0.12	
	Elevated	7	(3.1)	0.2		(0.1–1.3)

CI, confidence interval; CTPA, computed tomography pulmonary angiography; *n*, number of CTPA studies; OR, odds ratio

Patients with SCD were four times more likely to have suboptimal contrast opacification of the pulmonary artery on CTPA than those in the control group. In particular, 25.4% of SCD patients had suboptimal scans. Female patients had a lower suboptimal scan rate than their male counterparts (10.4% vs 22.0%; $p < 0.05$). No significant differences were found in the proportion of suboptimal scans according to age group ($p > 0.05$) (Table 4).

Multivariable binary logistic regression analysis was conducted to identify the independent factors associated with suboptimal CTPA studies. The model revealed that women were 50% less likely (OR = 0.5; 95% CI: 0.3–0.8) to have suboptimal scans. Patients with SCD were 4.4 times more likely (OR = 4.4; 95% CI: 2.4–8.3) to have suboptimal scans than those in the control group (Table 5).

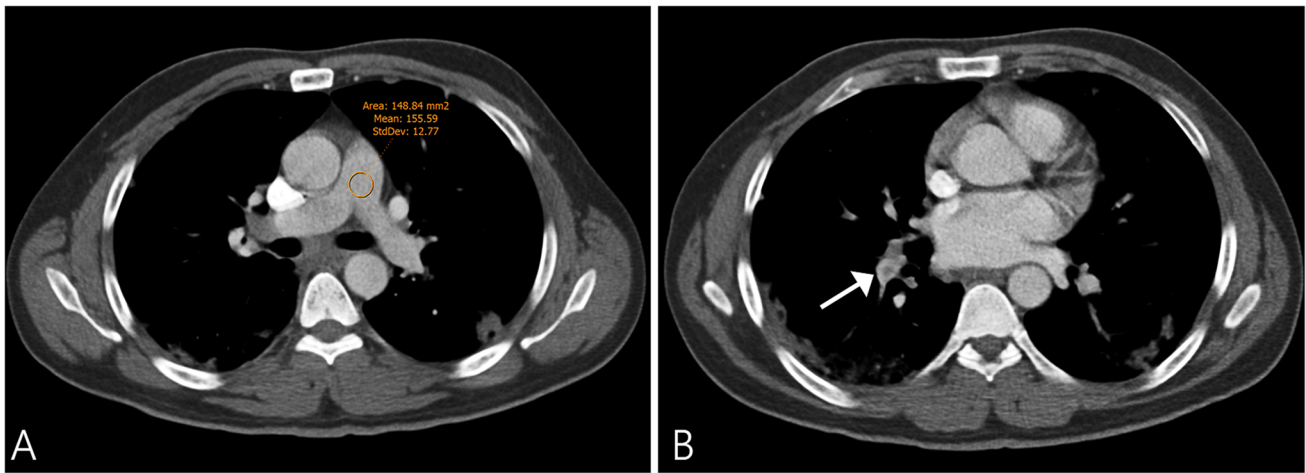


Fig. 1 Axial CT pulmonary angiography images in the thromboembolism-specific window of a 44-year-old man with sickle cell disease and recent recovery from COVID-19 are presented. The images show

inadequate contrast enhancement in the pulmonary artery of 156 HU (panel A) and a faint filling defect (arrow) within the right interlobar pulmonary artery consistent with pulmonary embolism (panel B)

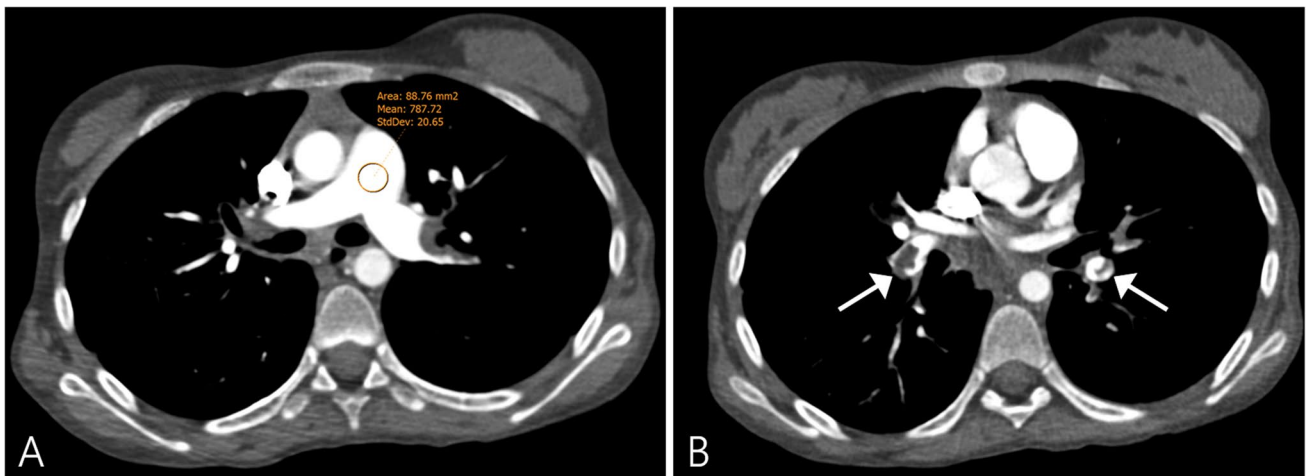


Fig. 2 Axial CT pulmonary angiography images in the thromboembolism-specific window of a 20-year-old woman without sickle cell disease after recovery from cardiac arrest are presented. The images show optimal contrast enhancement in the pulmonary artery of 788

HU (panel A) and clear filling defects (arrows) within the main pulmonary arteries bilaterally consistent with pulmonary embolism (panel B)

Discussion

The present study aimed to investigate the positive rate of CTPA and to quantitatively assess the quality of contrast opacification of the pulmonary arterial vasculature. The positive rate for PE was found to be comparable to that of the control group. However, patients with SCD had a significantly higher proportion of suboptimal scans.

The overall positive rate of CTPA was markedly below the standard recommended by the Royal College of Radiologists. Previous studies have reported widely divergent

positive rates of CTPA between different countries and institutions, ranging from approximately 1 to 34% [19–21]. Several factors have been linked to a lower positive rate of CTPA. Importantly, clinical scoring systems, such as the Wells criteria for PE, are not routinely applied despite the recommended guidelines [22, 23]. The practice of defensive medicine could be a relevant underlying factor. Given the large number of studies that have demonstrated an increased risk of thromboembolic events in SCD [24–26], a higher positive rate of CTPA in SCD was expected. However, this study showed that the SCD group had a positive rate similar to that of the control group. This

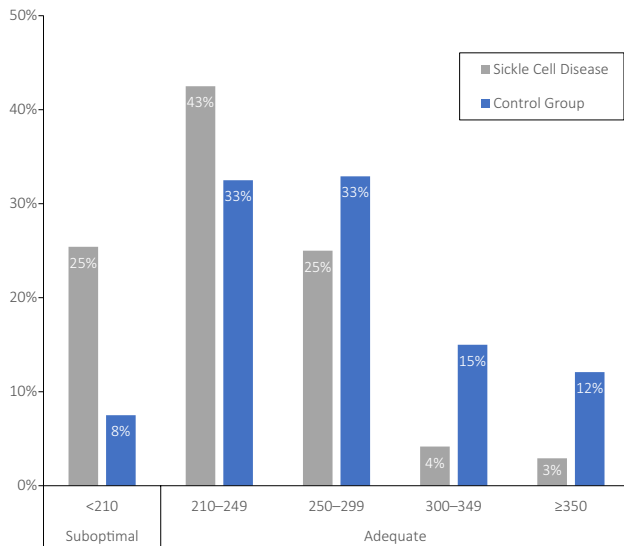


Fig. 3 Comparison of contrast opacification in the pulmonary artery between the sickle cell disease and control groups

finding could be related to the lower threshold to perform imaging studies in SCD, leading to an increased number of negative scans. Furthermore, the higher proportion of suboptimal scans in SCD can result in a higher number of false-negative scans, as most PEs in SCD involve the peripheral vasculature [27, 28], which requires high-quality scans for detection. The positive rate of CTPA in the control group of this study may not be representative of the general population of patients who underwent CTPA, as they were matched in age to the SCD group, which has a younger age profile [28].

The findings revealed that SCD patients had a higher tendency to have suboptimal scans due to inadequate contrast opacification of the pulmonary arterial vasculature. The results are consistent with the study by Jensen et al. [15], who found that almost 75% of SCD patients had a mean contrast enhancement of less than 250 HU in the pulmonary artery compared to 32% of patients in the control group, although both groups had a similar contrast volume and infusion rate. The reason for the inadequate contrast opacification of the pulmonary arterial vasculature in SCD remains unclear. However, that study postulated that altered cardiovascular dynamics in SCD seem to influence the contrast dynamics [15].

Various measures were recommended to mitigate the effects of inadequate contrast opacification of the pulmonary arterial vasculature in SCD. First, increasing the infusion rate with the use of fenestrated catheters may improve image quality without increasing the iodine load delivered [29]. Second, lowering kVp can improve image quality but at the expense of increasing image noise [30]. Third, obtaining the scan during the expiratory phase can eliminate transient enhancement artifacts [31]. However, future research is needed to assess image quality in SCD after implementing some of these strategies.

Ventilation-perfusion scintigraphy is a viable imaging option, particularly for stable patients with normal chest radiographs [32]. Compared to CTPA studies, ventilation-perfusion scintigraphy exposes patients to less radiation and does not require intravenous contrast administration [33]. This is especially critical for patients with SCD, who are typically young [28]. Up to 10% of SCD patients who undergo imaging studies for PE require a second study

Table 4 Rate of suboptimal CTPA studies according to age, sex, and sickle cell disease

Variables	Categories	Suboptimal scans (n=79)				p value
		n	(%)	OR	(95% CI)	
Age group (years)	18–35	34	(18.0)	Reference group		0.28
	36–50	41	(17.4)	1.0	(0.6–1.6)	
	51–65	3	(7.1)	0.4	(0.1–1.2)	
	> 65	1	(7.7)	0.4	(0.1–3.0)	
Sex	Male	55	(22.0)	Reference group		< 0.01
	Female	24	(10.4)	0.4	(0.2–0.7)	
Charlson Comorbidity Index	0	59	(19.5)	Reference group		0.13
	1–2	16	(11.3)	0.5	(0.3–1.0)	
	3–4	2	(9.1)	0.4	(0.1–1.8)	
	> 4	2	(15.4)	0.8	(0.2–3.5)	
Sickle cell disease	No	18	(7.5)	Reference group		< 0.01
	Yes	61	(25.4)	4.2	(2.4–7.4)	

CI, confidence interval; CTPA, computed tomography pulmonary angiography; n, number of CTPA studies; OR, odds ratio

p values are in bold if statistically significant

Table 5 Binary logistic regression analysis for suboptimal CTPA studies

Variable	Adjusted OR	(95% CI)	<i>p</i> value
Age group	18–35	Reference group	
	36–50	1.0	(0.7–1.7) 0.91
	51–65	0.3	(0.1–1.5) 0.16
	> 65	0.3	(0.1–2.8) 0.41
Female sex	0.5	(0.3–0.8)	0.01
Sickle cell disease	4.4	(2.4–8.3)	< 0.01
Hemoglobin level (g/dL)	1.0	(0.9–1.2)	0.83

CI, confidence interval; *CTPA*, computed tomography pulmonary angiography; *OR*, odds ratio

p values are in bold if statistically significant

within 90 days of the initial study [32], further emphasizing the need to minimize radiation exposure.

While this study is the largest to date to investigate the positive rate and image quality of CTPA studies in patients with SCD, it is not without limitations. The retrospective nature of the study is an important limitation. For instance, some patients may have undergone a scan with certain modifications to the standard scanning protocol (e.g., different catheter sizes), and this information was not readily available. Additionally, the lack of subjective assessment of the scans is another limitation, as other artifacts may negatively impact the diagnostic accuracy of the scan, despite adequate contrast opacification of the pulmonary arterial vasculature. There are several types of artifacts that can have a negative impact on the quality of CTPA studies. These include motion artifacts caused by breathing or other movements during the scan, transient interruption of contrast, streak artifacts that can be related to the contrast material in the superior vena cava, and inadequate contrast enhancement of the pulmonary vasculature adjacent to areas of parenchymal disease [34].

Conclusions

This study found a relatively low positive rate of CTPA in both SCD patients and the control group. However, SCD was significantly associated with suboptimal image quality due to inadequate pulmonary arterial contrast enhancement. Further research is needed to explore potential strategies for enhancing the quality of CTPA in SCD patients. Such investigations may pave the way for developing a customized imaging protocol for this patient population.

Abbreviations *CI*: Confidence interval; *CTPA*: Computed tomography pulmonary angiography; *HU*: Hounsfield unit; *IQR*: Interquartile range; *OR*: Odds ratio; *PE*: Pulmonary embolism; *SCD*: Sickle cell disease

Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate All methods were implemented in accordance with the Declaration of Helsinki, and the study was approved by the Ethics Review Committee. The requirement for informed consent was waived by the Ethics Committee of the Salmaniya Medical Complex in Bahrain because of the retrospective nature of the study, and no personal identification data were requested or stored.

Consent for publication Not applicable.

Conflict of interest The authors declare that they have no conflict of interest.

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