



# Maximum Venous Diameter is a Simple and Objective Measurement to Characterize Clinical Varicoceles

Arunan Sujenthiran<sup>1\*</sup>, Saad Abumelha<sup>2,3</sup>, Tet Yap<sup>1,2</sup>, Fahad Al Mashat<sup>2</sup>, Alex Kirkham<sup>4</sup>, Miles Walkden<sup>4</sup> and Suks Minhas<sup>2</sup>

<sup>1</sup>Department of Urology, St. George's Hospital and Medical School, UK

<sup>2</sup>Department of Urology, University College Hospital, UK

<sup>3</sup>Department of Surgery, Division of Urology, King Abdulaziz Medical City, Saudi Arabia

<sup>4</sup>Department of Radiology, University College Hospital, UK

## Abstract

**Purpose:** There are no diagnostic recommendations for the evaluation of men prior to therapeutic intervention for clinical varicoceles. The aim of this study was to define a simple and reliable hemodynamic parameter predicting the presence of reflux in clinical varicoceles (grade II/III) compared to the gold-standard of venography.

**Methods:** Data were retrospectively collected on men presenting to a tertiary referral center with subfertility/infertility, testicular pain or palpable mass over an 11-year period (2004-2015). Men with clinical varicoceles (defined as grade II/III) underwent color doppler ultrasound (CDU) and maximum venous diameter (MVD) was measured and correlated to reflux at venography, at the time of therapeutic embolization. Receiver-operator characteristic analyses identified the threshold MVD to detect reflux.

**Results:** A total of 107 men (70 unilateral, 37 bilateral) underwent CDU. From all, 144 testis units were included with a mean MVD of 3.5 mm (range 2 mm to 7 mm). CDU-reflux is demonstrated in 108 of 144 (75.0%) testes and 97 testes underwent venography of which 73 (75.3%) had demonstrable reflux. MVD in testes with venography-detected reflux was 4.0 mm (range 2 mm to 7 mm) compared to 2.7 mm (range 2 mm to 4 mm) in those without reflux ( $p < 0.01$ ). The optimal MVD for discriminating men with and without venography-diagnosed reflux was 3.0 mm (sensitivity-95.9%, specificity-58.3%, correctly-classified 86.6%, AUC=0.86). MVD  $\geq 3$  mm was a more accurate discriminator for identifying patients with venography-reflux compared to CDU-reflux alone (correctly-classified 82.5%, AUC=0.73).

**Conclusions:** A threshold value MVD  $\geq 3$  mm accurately identifies more men with proven venography-reflux than using CDU-detected reflux. MVD is a simple parameter that can be used to stratify men with clinical varicoceles, who may benefit from therapeutic intervention.

**Keywords:** Varicocele; Testes; Reflux; Ultrasonography; Doppler

## Introduction

A varicocele is defined as an abnormal venous dilatation of the pampiniform plexus of veins and is present in approximately 15% of the general population and in up to 35% of men evaluated for infertility [1,2]. The etiology of varicoceles is not fully understood but the condition is associated with anomalous reflux of blood into the pampiniform plexus. It has been suggested that the ensuing venous dilatation and stasis leads to an increase in scrotal temperature. Other pathological mechanisms proposed include testicular venous hypertension, autoimmunity, reflux of adrenal catecholamines and the so called nutcracker phenomenon [3]. However, it appears that venous reflux is the main underlying mechanism leading to the pathological effects on testicular function [4,5].

Varicoceles are commonly diagnosed by physical examination (PE) and graded according to the classification published by Dubin and Amelar [6] and later updated by the World Health Organization [7]. Clinical varicoceles are those detectable by visual inspection or palpation associated with anomalous reflux. Subclinical varicoceles are those that cannot be detected by PE alone but rely on adjunctive diagnostic modalities for detection, although the pathological significance of the

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### \*Correspondence:

Arunan Sujenthiran, Department of Urology, St. George's Hospital and Medical School, Blackshaw Road, London, SW19 0QT, UK, Tel: 020 78696645; Fax: 020 78696644; E-mail: asujenthiran@doctors.org.uk

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**Table 1:** Demographics, colour doppler ultrasound (CDU) and venography findings in men with grade II or III varicoceles.

No. Testes units	144	
Age (years)		
	20-29	21 (14.5)
	30-39	79 (54.9)
	>40	44 (30.6)
Venous Diameter (mm)		
	<2.5	12 (8.3)
	2.5-2.9	27 (18.8)
	3.0-3.9	48 (33.3)
	>4.0	57 (39.6)
CDU		
	Reflux absent	36 (25.0)
	Reflux present	108 (75.0)
Venography (97 testes)		
	Reflux absent	24 (24.7)
	Reflux present	73 (75.3)

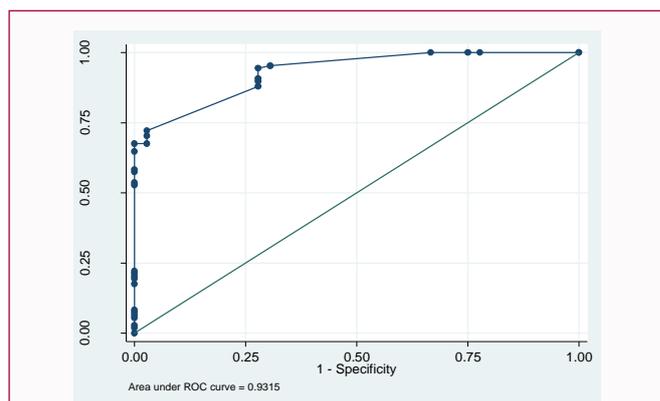
subclinical sub-type is unknown. However, contemporary guidelines do not advocate the treatment of subclinical varicoceles [8].

The significance of varicoceles and their treatment in sub-fertility remains controversial. A meta-analysis reported that although varicocelectomy has well-established efficacy in improving seminal parameters in sub-fertile men with clinical (palpable or visible) varicoceles, the impact of treatment on pregnancy rates has not been confirmed [9]. The importance of reflux is reinforced by studies showing reflux prior to intervention correlated with an improvement in seminal parameters [10,11]. For subclinical varicoceles current data suggests that repair for male factor infertility is not beneficial [9].

Guidelines from the European Association of Urology and American Urological Association recommend initial diagnosis of a varicocele should be ascertained by PE but there is no consensus on whether ultrasound should be used in all cases or only when PE is inconclusive [8,12]. Although PE is the standard diagnostic method of detection for varicoceles, it is subjective, limited by inter-physician variability and does not determine reflux. Furthermore, diagnostic ultrasound can exclude other significant pathologies in men who present with testicular pain prior to an intervention [13].

Several diagnostic modalities in addition to PE exist to detect varicoceles [14]. Venography is established in many studies as the gold standard in detecting venous reflux but is invasive and not routinely used as a diagnostic tool [15]. Color doppler ultrasound (CDU) is the most commonly used method for detection and classification of varicoceles [16]. It has greater diagnostic accuracy compared to PE alone but is also limited by being operator-dependent [14,17]. A number of studies have evaluated the predictive value of PE and CDU parameters including venous diameter (VD) at diagnosing CDU-reflux [18-23], but a consensus threshold value to define clinical varicoceles using VD does not exist. Various CDU-based classification systems have been suggested with the most commonly used by Chiou et al. [23] and Sarteschi [24]. However, these systems differ from each other, remain complex and are not routinely used in clinical practice.

VD is an easily obtainable simple measurement but studies



**Figure 1:** Receiver-operator character (ROC) analysis for venous diameter (VD) and colour doppler ultrasound (CDU)-detected reflux: 144 testes units underwent CDU and the optimal VD threshold was  $\geq 2.7$  mm with an area under the ROC curve of 0.93.

comparing this measurement to the gold standard of venography are limited. The objectives of this study were to determine whether VD and venous reflux on CDU correlated with a clinical varicocele (grade II/III) confirmed with venography. We also sought to define a measurement of maximum venous diameter (MVD) that can be used as a diagnostic threshold for men presenting with clinical varicoceles.

## Patients and Methods

In this retrospective clinical review, men presenting to a tertiary referral center for sub-fertility/infertility, testicular pain or a palpable mass were assessed for the presence of a clinical varicocele from July 2004 to May 2015. Institutional review was not required for this study but the study was performed strictly according to the clinical governance regulations and policies at our institution. A clinical varicocele was defined as grade II or grade III on PE according to WHO criteria [7].

### Technique of color doppler ultrasound

All men underwent CDU scanning by uro-radiologists using a high frequency (14 MHz) linear probe on appropriate scrotal settings in the supine position. Parameters assessed were testicular volume, MVD and the presence or absence of venous reflux. MVD was defined as diameter of the largest vein in the pampiniform plexus and was measured at rest. The presence or absence of reflux was evaluated by assessing augmentation on Valsalva also in the supine position as part of our standardized protocol.

### Venography and embolization

Of all subjects, 72 men (67%) elected to have radiological embolization, all of whom underwent renal vein and gonadal venography as part of the procedure. Venography was performed via a right internal jugular vein approach in the supine position. Demonstration of retrograde contrast flow to the gonadal vein when the patient performed Valsalva was the criterion for venography-reflux. If reflux was not demonstrated on venography then embolization was not performed.

### Statistical analysis

MVD was sub-divided into varicoceles of less than 2.5 mm; 2.5 mm to 3.0 mm; 3.0 mm to 4.0 mm and greater than 4 mm. The optimal threshold, sensitivity and specificity for MVD were determined by receiver-operator characteristic (ROC) analyses. The optimal operating point of the ROC curve was chosen as the value

that produced the highest percentage of correctly classified patients. Mann-Whitney U test was used to compare groups with reflux present and absent. A logistic regression model was generated and univariate analysis was performed to assess association of study variables with venography-reflux ( $p < 0.01$  was considered statistically significant). Stata® version 14 (Stata Corp, College Station, Texas, USA) was used for all statistical calculations.

## Results

In total, 107 men underwent CDU for clinical varicoceles (defined as grade II or III) on PE and among all, 70 men had a unilateral left-sided varicocele and 37 men had bilateral varicoceles. In total, 144 testis units were included in the study. The mean age was 37 years (range 20 to 60 years) and mean MVD was 3.5 mm (range 2 mm to 7 mm) (Table 1).

### Color doppler ultrasound

Among 144 testes, 108 (75%) were found to have reflux on CDU. The mean MVD in men with CDU-diagnosed reflux was 3.9 mm (range 2.5 mm to 7 mm) compared to 2.5 mm (range 2.0 mm to 3.3 mm) in those without reflux (Mann-Whitney U test,  $p < 0.01$ ).

A ROC analysis identified the optimal threshold value for discriminating men with and without CDU-diagnosed reflux as  $\geq 2.7$  mm (sensitivity 94.4%, specificity 72.2%, correctly-classified 88.9%, AUC=0.93) (Figure 1).

### Venography

At the time of therapeutic embolization, 97 testes units underwent venography to assess venous incompetence. Of these, 78 had reflux present on CDU and 19 did not. Of the 19 testes without CDU-reflux, 13 did not demonstrate reflux on venography and 6 were found to have reflux on venography (Table 2A-2C).

Out of 97 testes 73 (75.3%) underwent venography displayed reflux on venography and underwent embolization. The MVD in men with venography-detected reflux was 4.0 mm (range 2 mm to 7 mm) compared to 2.7 mm (range 2 mm to 4 mm) in those without reflux (Mann-Whitney U test,  $p < 0.01$ ).

ROC analysis identified the optimal threshold value for discriminating men with and without venography diagnosed reflux as  $\geq 3.0$ mm (sensitivity 95.9%, specificity 58.3%, correctly-classified 86.6%, AUC=0.86) (Figure 2).

**Table 2A:** Comparison of testes with venous diameter  $\geq 3$  mm and venography-detected reflux.

Maximum venous diameter	Venography-reflux		Total
	absent	present	
<3mm	14	3	17
$\geq 3$ mm	10	70	80
Total	24	73	97

Correctly classified: 84/97 (86.6%), AUC=0.857.

**Table 2B:** Comparison of testes with CDU-detected reflux and venography-detected reflux.

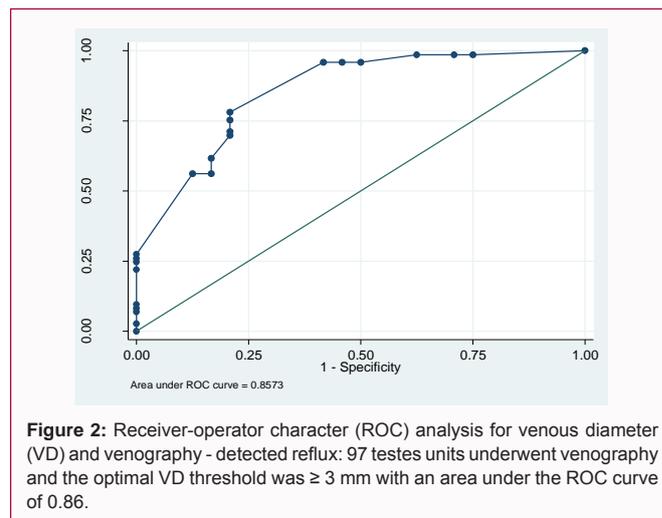
CDU-reflux	Venography-reflux		Total
	absent	present	
absent	13	6	19
present	11	67	78
Total	24	73	97

Correctly classified: 80/97(82.5%), AUC=0.7297.

**Table 2C:** The effect of a maximum venous diameter with a threshold of 3 mm and CDU-reflux on the presence of venography reflux.

	Venography-reflux		Total
	absent	present	
VD<3 mm & CDU-reflux absent	11	3	14
VD<3 mm & CDU-reflux present	3	0	3
VD $\geq 3$ mm & CDU-reflux absent	2	3	5
VD $\geq 3$ mm & CDU-reflux present	8	67	75
Total	24	73	97

Correctly classified: 78/97 (80.4%).



Among 97 testes 84 (86.6%) were correctly classified as having venography-reflux using a threshold MVD  $\geq 3$  mm compared to 80 out of 97 testes (82.5%) using absence or presence of CDU-reflux. A combination of MVD  $\geq 3$  mm and CDU-reflux did not increase the proportion of correctly classified men with reflux on venography (78 out of 97 testes (80.4%) compared to MVD alone (Table 2A-2C).

### Logistic regression

A logistic regression model was generated to determine factors predicting presence of venography-reflux. On univariable analysis MVD  $\geq 3$  mm (OR 32.7, 95% CI 7.96-134.1,  $p < 0.001$ ) and CDU reflux (OR 22.3, 95% CI 6.79-73.7,  $p < 0.001$ ) were significant predictors of venography reflux. Age (OR 0.96, 95% CI 0.90-1.01,  $p = 0.15$ ) was not significantly related to the presence of venography-reflux.

## Discussion

There is currently no universally accepted definition for a clinical varicocele based on ultrasound criteria, and existing classifications remain highly complex. This study reports on a large series of patients who had both MVD measured on ultrasound and reflux diagnosed on venography. It demonstrates that MVD is a simple hemodynamic parameter, which can be used to correctly identify most patients with reflux on venography and thus those patients more likely to benefit from treatment.

In the current study, ultrasound imaging was performed in all men before venography allowing exclusion of other pathological causes of scrotal pain and is supported in a previous study [25]. It can also be used to document the presence of reflux with the assumption that reflux is the mechanism leading to the pathological effects of a varicocele. In support of this, studies have demonstrated the absence

**Table 3:** Studies comparing physical examination (PE), venous diameter (VD), scoring systems to colour doppler ultrasound (CDU) reflux.

Author	Type of Study	Number of men/ Definitions	Type(s) of Imaging used	Radiological criteria used	Conclusion
Pilatz et al. [18]	Prospective Comparison of varicoceles on PE to CDU diagnosed VD & reflux	217 (129 clinical varicoceles/88 controls) Clinical varicocele: PE (standing) and WHO criteria: Grade I, II & III	CDU	VD>2.45 mm at rest (supine) VD>2.95 mm during Valsalva (supine)	Clinical varicoceles can be predicted using VD cut-point values of 2.45 mm in rest or 2.95 mm during Valsalva. Sensitivity >80%, Specificity >80%.
Hoekstra et al. [19]	Prospective Comparison of palpable & non-palpable varicoceles (on PE) to VD of internal spermatic vein on CDU.	78 men 156 testicles (56 with palpable internal spermatic vein)	CDU	Internal spermatic VD	Internal spermatic vein with diameters <3 mm are non-palpable on PE. US reversal of flow occurred in all cases when VD >3.5 mm.
Aydos et al. [20]	Retrospective Comparison of CDU and physical examination	39 men 18 men clinical varicocele 21 men without clinical varicocele	CDU	VD	In men with varicocele VD >2 mm. In men without varicocele VD <1.8 mm
Orda et al. [21]	Prospective Comparison of left spermatic cord vein diameter in clinical varicoceles (physical examination) to controls.	20 men (clinical varicoceles) 18 men (controls)	B-mode gray scale ultrasound	VD	Clinical varicoceles >4.5 mm (standing position) and >5.7 mm during Valsalva.
Wolverson et al. [22]	Retrospective Comparison of scrotal vein diameter in clinical varicocele (palpable physical examination) and controls	13 men	Doppler Ultrasound	VD	Clinical varicoceles ranged from 2 mm – 5 mm
Chiou et al. [23]	Prospective Comparison of CDU venous diameter to clinical varicocele (physical examination – negative/uncertain/positive) Versus new CDU criteria	64 men (127 testis) 59 testis positive 57 testis negative 11 testis uncertain	CDU	<b>Traditional:</b> VD >3 mm <b>Scoring system:</b> VD, sum of diameter of veins, change of flow during Valsalva	<b>Traditional:</b> sensitivity 53% & specificity 91%. <b>Scoring system:</b> sensitivity 93% & specificity 85%

of reflux in men who have had a varicocele treated successfully following surgery [26]. Historically, operative intervention for clinically palpable varicoceles has been based solely on PE findings without further diagnostic imaging to detect reflux. This study has shown that 1 in 4 men did not have reflux on CDU (25%) and venography (24.7%) and would have potentially been over-treated if they were operated on the basis of PE alone.

In this study, a threshold value  $\geq 3$  mm on univariate logistic regression was shown to be a stronger predictor than CDU-detected reflux in predicting reflux diagnosed by venography. The presence of CDU-detected reflux in addition to a MVD  $\geq 3$  mm did not improve diagnostic accuracy.

A consensus threshold value to define the presence of a varicocele using VD does not exist (Table 3). The studies conducted in Table 3 have used values ranging from 2.0 mm to 5.7 mm to define a clinical varicocele. It is difficult to interpret these values given the heterogeneity of subjects and conditions used to perform CDU. The largest study reported that varicoceles (Grade I to III) detected on PE could be predicted using a VD threshold of 2.45 mm at rest or 2.95 mm during Valsalva with a sensitivity and specificity above 80% [18]. Hoekstra and Witt [19] used CDU to show that reversal of flow was only present when the internal spermatic vein diameter was greater than 3.5 mm and did not occur below 2.5 mm. Other studies have identified different thresholds of VD also using CDU-reflux as a comparative standard alone without comparison to venography (Table 3) [20-22]. The present study has shown that CDU-reflux accurately classifies fewer patients than venous diameter  $\geq 3$  mm. Venography is also widely acknowledged in the literature to be more reliable than CDU at detecting reflux though is used less frequently due to its invasiveness, cost and contrast exposure [15,27].

Three other studies have utilized venography in their diagnostic protocol (Table 4). Trum et al. [14] reported a sensitivity and specificity of 97% and 94%, respectively of detecting varicoceles using reflux of greater than 1 second on CDU in comparison to venography-reflux. This study reported on grade I-III varicoceles and did not report

on the use of VD as a predictive parameter. Reflux of greater than 1 second on CDU correctly classified 95.2% of the 31 patients who underwent venography. The study was limited by sample size and also underestimating the number of false positives and false negatives as bilateral varicoceles were counted as having reflux even if only one testicle demonstrated reflux. Ten percent of varicoceles in this study were bilateral therefore the actual percentage of correctly classified patients was lower than stated. The current study avoids this by presenting results for individual testis units. Results from the current study showed a threshold of MVD  $\geq 3$  mm correctly predicted more patients with venography-reflux than those with CDU-reflux (86.6% versus 82.5% correctly classified, respectively). The current study also only included clinical varicoceles (grade II/III) since the pathological significance of grade I varicoceles remains controversial.

Eskew et al. [28] conducted a prospective study of 33 men and identified internal spermatic vein diameter as the most accurate predictor of venography-detected varicoceles. The authors reported 3.6 mm as the optimal cut-off point with an accuracy of 63%. The current study derived the optimal threshold from a larger sample and found 3mm to be more accurate (86.6%) than the value used by Eskew. Petros et al. compared CDU to venography in 14 men and reported that CDU-reflux had an accuracy of only 82.4% compared to venography (16) (Table 3).

Other studies have suggested that VD alone is not sufficient to detect the presence of a varicocele. Kocakoc et al. [29] advocated the measurement of flow volume since it reflects a combination of venous diameters, duration and velocity of reflux. Chiou et al. [23] proposed a scoring system incorporating MVD, the sum of the diameters of the veins in the plexus and change of flow on Valsalva which was shown to be more sensitive and specific at diagnosing varicoceles compared to using a venous diameter measurement of 3 mm. Neither of these studies however compared findings to venography-detected reflux. Reproducibility of doppler measurements makes the application of this scoring system to routine clinical practice more challenging and difficult. In the absence of a universally agreed validated classification system for assessing reflux, MVD provides a simple and objective

**Table 4:** Studies comparing to physical examination (PE), venous diameter (VD), colour Doppler ultrasound (CDU) reflux to venography reflux.

Author	Type of Study	No. of pts. / Definitions	Type(s) of Imaging used	Radiological criteria used	Conclusion
Trum et al. 1996 [14]	Prospective Assess accuracy of CDU at detecting a varicocele compared to venography.	63 men CDU diagnosed varicocele if reflux present with or without Valsalva occurred for >1second. 31 men underwent venography.	CDU Venography	Pathological reflux on CDU if > 1 second.	CDU-reflux > 1second has a sensitivity of 97% and specificity of 94% at detecting varicocele compared to venography.
Eskew et al. 1993 [28]	Prospective Assess the ability of CDU to confirm diagnosis of clinical varicocele (from PE & venography)	33 men	CDU Venography	Internal spermatic vein diameter	Best predictor of varicocele was internal spermatic VD (supine, resting) Best cut-off point for venous diameter for a clinical varicocele was 3.6mm (63% accuracy)
Petros et al. 1991 Abstract only available [17]	Comparison of PE, CDU to venography in detection of varicoceles	14 men	CDU Venography	No data on CDU parameters	PE (71% detection rate of varicocele cf to venography) CDU (93% sensitivity/33% specificity) cf to venography) CDU-reflux: VD $\geq$ 2.7mm (94.4% sensitivity, 72.2% specificity) Venography-reflux: VD $\geq$ 3.0mm (95.9% sensitivity, 58.3% specificity)
Current Study 2017	Identifying optimal venous diameter threshold for CDU-detected reflux and venography-detected reflux	144 testes (CDU) 97 testes (venography)	CDU Venography	VD	

measure not confounded by previously mentioned factors.

The limitations to this study are that this is a single-center, retrospective and non-randomized study. Although we controlled for technique by using a standardized approach for both CDU and venography, there were certain factors that were not possible to control including room temperature which can affect venous diameter measurements. Furthermore, venography may be inaccurate in the diagnosis of reflux; inaccurate placement of catheter tip, performing venography under high pressure and anatomical variations can lead to false-positive and false-negative results [15,23,30].

Despite this, the current study has shown a threshold of  $\geq 3$  mm correctly classified 87% of patients with venography-detected reflux. This finding is comparable and in most cases superior to current existing parameters. There are no universally accepted criteria for the diagnosis of a clinical varicocele. Given that it is likely to be impossible to define criteria that are completely accurate, an attempt to simplify diagnostic radiological criteria currently used to define and ultimately treat varicoceles, with easily replicated and reproducible thresholds should be made. A threshold value for MVD  $\geq 3$  mm when compared to venography provides a simple and accurate method for identifying clinical varicoceles.

## Conclusions

Maximum venous diameter is a simple hemodynamic parameter that can be readily determined in patients with clinical varicoceles. This study has shown that a threshold value  $\geq 3$  mm can accurately predict reflux diagnosed by the gold standard of venography, whilst accurately stratifying men with clinical varicoceles, who may benefit from therapeutic intervention. The additional presence of CDU-detected reflux did not improve diagnostic accuracy.

## Authors Contribution

A Sujenthiran: Protocol/project development; Data collection or management; Data analysis; Manuscript writing/editing

S Abumelha: Data collection or management; Manuscript writing/editing

T Yap: Protocol/project development; Data collection or management; Data analysis; Manuscript writing/editing

F Al Mashat: Data collection or management; Manuscript writing/editing

A Kirkham: Protocol/project development; Manuscript writing/editing

M Walkden: Protocol/project development; Manuscript writing/editing

S Minhas: Protocol/project development; Data collection or management; Data analysis; Manuscript writing/editing

## Compliance with Ethical Standards

Institutional review was not required for this study but the study was performed strictly according to the clinical governance regulations and policies at our institution.

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