COMPARISON OF CONTRAST ENHANCEMENT AND IMAGE QUALITY USING DIFFERENT CONTRAST ADMINISTRATION PROTOCOLS FOR ROUTINE ABDOMINAL COMPUTED TOMOGRAPHY (CT) IN TWO CENTERS

DR POH CHOON SIAN

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR MASTER OF MEDICINE (RADIOLOGY)

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TABLE OF CONTENT

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

ABT	Automatic bolus tracking
AMDI	Advanced Medical and Dental Institute
BMI	Body mass index
BSA	Body surface area
CECT	Contrast-enhanced computed tomography
CM	Contrast medium
CT	Computed tomography
ECG	Electrocardiogram
FTD	Fixed time-delay
HU	Hounsfield unit
HUSM	Hospital University Sains Malaysia
IV	Intravenous
LBW	Lean body weight
PACS	Picture archiving and communication system
ROI	Region of interest
SD	Standard deviation
TBW	Total body weight
WBD	Weight based dosing

ABSTRAK

Latar belakang: Imbasan CT adalah prosedur pengimejan diagnostik yang menggunakan sinar-x untuk membina imej badan. Imbasan CT adalah kaedah pengimejan yang biasa digunakan dalam perubatan moden. Peneguhan kontras adalah komponen utama dalam imbasan CT berkontras (CECT) yang membantu membezakan struktur badan yang normal daripada yang tidak normal. Banyak faktor yang dapat mempengaruhi kualiti gambar CECT dan boleh dibahagikan kepada tiga kategori: pesakit, media kontras dan teknik imbasan CT. Kekurangan pemiawaian telah menyebabkan pelbagai protokol imbasan yang berlainan digunakan dalam bidang radiologi. Tujuan kajian ini adalah untuk membandingkan kesan dua protokol imbasan yang berbeza terhadap peneguhan kontras dan kualiti gambar imbasan CT abdomen berkontras.

Metod: Kajian keratan lintang dijalankan di Hospital Universiti Sains Malaysia (HUSM), Kota Bharu, Kelantan, Malaysia dan Institut Perubatan dan Pergigian Termaju (IPPT), Kepala Batas, Pulau Pinang, Malaysia ke atas 336 orang pesakit yang berumur 18 tahun ke atas dengan imbasan CT abdomen berkontras yang telah dilakukan antara bulan Januari 2017 hingga Disember 2019. Imbasan CT abdomen berkontras yang menggunakan protokol yang berbeza dikumpulkan secara retrospektif daripada kedua-dua pusat ini; 168 orang pesakit dari HUSM yang menggunakan protokol isipadu kontras tetap dengan penangguhan masa tetap, dan 168 orang pesakit dari IPPT yang menggunakan protokol isipadu kontras berdasarkan berat badan dengan penjejakan *bolus* secara automatik. Penilaian secara kuantitatif dilakukan dengan mengukur tahap peneguhan kontras di bahagian yang dinilai dan dihitung

dalam unit Hounsfield (HU). Nilai min HU daripada kedua-dua protokol akan dianalisa dengan menggunakan ujian-t tidak bersandar. Penilaian secara kualitatif dilakukan di mana gambar imbasan CT abdomen akan dinilai oleh pakar radiologi dengan menggunakan skala 4 markah. Nilai min markah kualitatif daripada kedua-dua protocol akan dianalisa dengan menggunakan ujian-t tidak bersandar.

Keputusan: Terdapat perbezaan min yang signifikan dari segi nilai peneguhan kontras (HU) di antara protokol isipadu kontras berdasarkan berat badan dengan penjejakan *bolus* secara automatik dan protokol isipadu kontras tetap dengan penangguhan masa tetap ($p<0,001$). Nilai peneguhan kontras min aorta dan vena portal lebih tinggi dalam protokol isipadu kontras berdasarkan berat badan dengan penjejakan *bolus* secara automatik. Terdapat juga perbezaan min markah kualitatif yang signifikan di antara kedua-dua protokol ($p =0.004$). Nilai min markah qualitatif adalah lebih tinggi dalam protokol isipadu kontras berdasarkan berat badan dengan penjejakan *bolus* secara automatik

Kesimpulan: Protokol isipadu kontras berdasarkan berat badan dengan penjejakan *bolus* secara automatik menunjukkan tahap peneguhan kontras yang lebih tinggi dan kualiti imbasan CT yang lebih baik berdasarkan pernilaian pakar radiologi dalam imbasan CT abdomen berkontras.

Kata kunci: imbasan CT abdomen berkontras, medium kontras, isipadu kontras berdasarkan berat badan, penjejakan bolus secara automatik.

ABSTRACT

Background: Computed tomography (CT) scanning is a diagnostic imaging procedure that uses x-rays to build images of the body. CT scanning is an extremely common imaging modality in modern medicine. Contrast enhancement is the key component in CT scanning which helps to distinguish abnormal from normal body structure. Numerous interacting factors can affect the quality of CECT images, which may be divided into three categories: patient, contrast medium and CT scanning. A lack of standardization has resulted in heterogeneous dosing regimens across radiology practices. The purpose of this study is to compare the effect of the two different scanning protocols mentioned above on the contrast enhancement and image quality of CECT abdomen.

Methods: A cross-sectional study was conducted in Hospital Universiti Sains Malaysia (HUSM), Kota Bharu, Kelantan, Malaysia and Advanced Medical and Dental Institute (AMDI), Kepala Batas, Penang, Malaysia on 336 patients aged 18 and above with contrast-enhanced CT (CECT) scan of abdomen between January 2017 and December 2019. Images of the CECT abdomen using different protocol were collected retrospectively from these two centres: 168 patients from HUSM, using fixed contrast volume with fixed time-delay technique, and 168 patients from AMDI using weight-based contrast volume with automatic bolus tracking technique. Quantitative assessment was performed by measuring the degree of enhancement in region of interest and were quantified in Hounsfield unit (HU). Mean enhancement values from each protocol was assessed and compared using independent t-test. Qualitative assessment was performed in which the images will be graded by radiologist using 4

points scale. Mean qualitative score from each protocol will be compared using independent t-test.

Results: A total of 336 participants were recruited for this study, which includes of 146 males and 190 females. The mean age of the participants is 41.51 years old from HUSM and 47.68 years old from AMDI. The result of the data showed that the mean weight of the participants is 54.55 kg from HUSM and 59.86 kg from AMDI. There was significant mean difference of enhancement value (HU) between weight-based contrast volume with automatic bolus tracking protocol and fixed contrast volume with fixed time-delay protocol ($p<0.001$). The mean enhancement values of aorta and portal vein was higher in weight-based contrast volume with automatic bolus tracking protocol. There was also significant mean difference of qualitative score between the two protocols (p value=0.004). The score was higher in weight-based contrast volume with automatic bolus tracking protocol.

Conclusion: Weight-based contrast volume with automated bolus tracking protocol demonstrate higher degree of contrast enhancement and significant better CT quality with higher grading by assessor in routine CECT abdomen.

Keywords: CECT abdomen, contrast medium, weight-based contrast volume, automated bolus tracking.

CHAPTER 1: BACKGROUND

1.1 Introduction

Computed tomography (CT) scanning is a diagnostic imaging procedure that uses x-rays to build cross-sectional images of the body. Cross-sections are reconstructed from measurements of attenuation coefficients of x-ray beams in the volume of the object studied. Once a number of successive cross-sectional images are collected by the machine's computer, they can be digitally "stacked" together to form a three-dimensional image of the patient that allows for easier identification and location of basic structures as well as possible tumors or abnormalities.

CT scanning is an extremely common imaging modality in modern medicine. With advancements in technology, it is rapidly replacing many diagnostic radiographic procedures. CT scanning has been widely used in aiding the management of patient. For example, CT scanning have played a fundamental role in the management of oncology patients. CT findings also have a substantial effect on the treatment management of patients with acute abdominal pain (Stoker J. *et al.*, 2009).

Problem Statement

Increasing demand has increased pressure on CT services and there is now increasing need to improve costs and efficiency whilst maintaining diagnostic quality (Perrin E. *et al*., 2018). Increased emphasis is now placed on patient preparation and patient specific acquisition protocols to reduce diagnostic errors (Perrin E. *et al*., 2018). Extensive research has been conducted using phantoms, computer simulations, and

human subjects to investigate the optimal method of dosing iodinated contrast material for use in contrast-enhanced CT of the abdomen and pelvis (Kondo H *et al*., 2013).

A lack of standardization has resulted in heterogeneous dosing regimens across radiology practices (Bae KT *et al*., 2010). For example, all the following are examples of contrast-enhanced CT (CECT) abdomen protocols that either have been studied recently or are in use in the United States:

- fixed-volume administration (Bae KT et al., 2010).
- linear volume-based dosing by total body weight (Yamashita *et al*., 2000).
- iodine based dosing by TBW (Ho LM *et al*., 2007)
- iodine based dosing by lean body weight (LBW) (Kondo H *et al.,* 2011)
- iodine-based dosing by either body surface area (BSA) or body mass index (BMI) (Kidoh M *et al.*, 2013)

In Hospital Universiti Sains Malaysia (HUSM), the CECT Abdomen is performed based on fixed contrast volume with fixed time-delay protocol as stated below:

- Injection of 100mL IV contrast iodinated contrast media (300 mg/ iodine/mL) with injection rate of 3mls/sec is given, followed by 50 mL saline chaser with injection rate of 3mls/sec.
- Images are acquired after 60 sec delay.

While in AMDI, the scanning protocol is based on weight-based contrast volume with bolus tracking technique as stated below:

- Weight based contrast volume: Iodinated contrast medium 300mg iodine/mL is used. Contrast amount is based on body weight (525mgI/kg).

Weight of patient	1st phase	2nd phase	Saline chaser
< 55kg	1.5g I/s for 5s	(Duration)s @ 1.2g I/s	30mls @3.2mls/s
56 – 95kg	1.7g I/s for 5s	(Duration)s @ 1.4g I/s	40mls @3.2mls/s
> 95kg	1.9g I/s for 5s	(Duration)s @ 1.5g I/s	50mls @3.2mls/s

Table 1 Weight-based contrast volume.

- Bolus tracking technique: Radio-opaque contrast media is injected into the patient via a peripheral intravenous cannula as per protocol. The volume of contrast is tracked using a region of interest (abbreviated "ROI") at the liver and then followed by the CT scanner once it reaches the level (50 Hounsfield unit). Images are then acquired.

Thus, the aim of this study is to compare the effect of the two different scanning protocols mentioned above on the contrast enhancement and image quality of CECT abdomen and their validity in clinical practice. We hope this study can be used in future as a guideline or reference in standardizing the iodinated contrast material administration protocol in CECT abdomen.

1.2 Objectives

1.2.1 General Objective

To study the effect of two different scanning protocols (weight-based contrast volume with automatic bolus tracking technique and fixed contrast volume with fixed time-delay technique) on the contrast enhancement and image quality of CECT abdomen.

1.2.2 Specific Objectives

1. To quantitatively evaluate the degree of contrast enhancement of the CECT abdomen between the two different scanning protocols based on the mean attenuation value (Hounsfield unit, HU) at the region of interest (ROI).

2. To qualitatively evaluate the image quality of the CECT Abdomen between the two different scanning protocols based on the subjective assessment of experienced radiologist using 4-point scale.

3. To compare the mean volume of administered contrast material between the two different scanning protocol.

4. To determine the optimal scanning technique and CM administration method to achieve satisfactory image quality for routine abdominal CT examinations.

1.3 Null Hypothesis

There is no significant difference in the contrast enhancement and image quality of the abdominal CT between two different scanning protocols.

1.4 Research Question

Is there any significant different in the contrast enhancement and image quality of the CECT abdomen between the two different scanning protocols (weight-based contrast volume with automatic bolus tracking technique and fixed contrast volume with fixed time-delay technique) that are practiced in two different centers?

CHAPTER 2: LITERATURE REVIEW

2.1 Contrast enhancement

Contrast enhancement is the key component in CT scanning which helps to distinguish abnormal from normal body structure. It may refer to any method of exaggerating the visible difference between adjacent structures on imaging by administering contrast media or agents. Usefulness of CECT for the diagnosis of hepatic diseases is widely recognized and the technique is employed at many centers (Svensson A *et al*., 2012).

2.2 Factor affecting contrast enhancement

Numerous interacting factors can affect the quality of CECT images, which may be divided into three categories: patient, contrast medium and CT scanning. Contrast medium pharmacokinetics and contrast enhancement are determined solely by the patient and contrast medium factors; and are independent from the CT scanning technique (Bae KT *et al.,* 2010).

2.2.1 Patient related factors

The key patient-related factors affecting contrast enhancement are patient body size (weight) and cardiac output. Other patient factors that are considered less influential includes age, sex, venous access, renal function, and various pathologic condition. Body weight is considered the most important patient-related factor affecting the magnitude of vascular and parenchymal contrast enhancement. To

maintain a consistent level of contrast enhancement in larger patient, one should consider increasing the overall iodine dose delivery by increasing contrast medium volume or concentration. The most important patient-related factors affecting the timing of contrast enhancement is cardiac output. When cardiac output decreases, contrast medium arrives slowly and clears slowly, resulting in delayed contrast medium arrival and delayed but stronger peak arterial and parenchymal enhancement (Bae KT *et al.,* 2010).

2.2.2 Contrast medium related factors

Keys factors related to contrast medium to be considered in contrast enhancement include injection duration, injection rate, injection bolus shape, contrast medium volume, concentration and use of saline flush. Injection duration is the most important injection-related factor affecting CT scan timing (Bae KT *et al.,* 2010). When contrast medium volume is tailored to the patient's body weight, a fixed injection duration protocol is advantages over a fixed injection rate protocol because the scan timing can be more easily standardized (Heiken JP *et al*., 1995). The shape of injected contrast material bolus can be tailored to bring about a desired enhancement pattern. Uniform prolonged arterial enhancement may be achieved with either an individually customized biphasic injection or with the exponentially decelerated multiphasic injection method. A saline flush improves contrast enhancement and the efficiency of contrast medium use, reduces artifact and is particularly beneficial when the total volume of contrast medium is small (Bae KT *et al.,* 2010).

2.2.3 CT scanning related factors

CT scanning factors play a significant role by enabling us to acquire contrast-enhanced images at the specific time point. Scanning parameters critically affecting contrast enhancement include scan duration, scan direction, determination of the contrast material arrival time relative to the scan delay, and scan delay from the start (or completion) of contrast medium injection to the initiation of scan. Scan duration information is crucial for the calculation of the injection duration and scan timing. For a long scan, an extended injection is likely required. Contrast material arrival time can be estimated either by using a test-bolus or bolus-tracking method (Bae KT *et al.*, 2010).

The two main scanning parameters to be considered in CT scanning would be tube voltage (kVp) and tube current (mA). Tube voltage is the electrical potential applied to each electron as it accelerates in the x-ray tube. As the electron accelerates across the tube, it gains energy and that energy is released as heat and x-rays when the electron interacts with the anode. The higher the kilovoltage setting, the higher the average energy of the x-rays (MB Afifi *et al.*, 2020). Tube voltage setting does affect the contrast enhancement in CT scanning. Use of lower CT tube voltages yields stronger contrast enhancement for a given injection of contrast medium (Bae KT *et al.*, 2010). However, when a lower tube voltage protocol is used without an increase in tube current, the image noise will increase, especially for larger patient. Milliamperes are a measure of the rate at which electrons are flowing through the x-ray tube. It is generally useful to set the mA as high as possible to minimize scanning time. In a study conducted by Mohamed Bahaaeldin Afifi et al. found that at CT

voltages 120 and 140 kV the differences are negligible whatever is the CT current value (MB Afifi *et al.*, 2020).

2.3 Contrast dosing regimens

Various contrast dosing regimens have been used across radiology practices. Historically a fixed dose of intravenous iodinated contrast medium has been used for portal venous phase abdominal CT (Kondo H. *et al*., 2013). However, with increasing body mass indices (BMI), the patient populations scanned nowadays have a wider weight distribution than ever. This resulted in a subjective variation in abdominal organ enhancement depending on patient weight. Patients of low weight would have examinations with excessive iodinated contrast, whereas those of large weight had examinations with insufficient iodinated contrast (Perrin E. *et al*., 2018).

2.4 Weight-based contrast administration

Weight-based contrast injection can provide multiple benefits during imaging. First, larger patients are often underdosed with respect to intravenous (IV) contrast, and thus, weight-based dosing (WBD) can improve contrast enhancement (Kondo H et al., 2010). Second, smaller patients typically receive more contrast than needed, which can potentially increase the risk of contrast-induced neuropathy in at-risk patient populations (Kondo H et al., 2011). In smaller patients, there are also potential cost savings, especially when lower kilovoltage protocols are used because similar enhancement can be obtained at lower IV contrast doses (Kondo H et al., 2013).

2.5. Optimization of contrast enhancement.

To optimize the detection of abdominal lesions, whilst minimizing cost, Yamashita et al. have recommended using a patient tailored approach to the administration of contrast material (Yamashita et al., 2000). Further researchers have encouraged the use of weight-adapted protocols and support the need of adapting contrast media dose to allow for patients' differing body habitus (Awai K et al., 2016). Studies have shown that maximum hepatic enhancement is inversely related to body weight (Heiken JP et al., 1995). However, Benbow and Bull demonstrated that, compared to a fixed dose protocol, adaptive contrast protocols could reduce liver contrast enhancement variability between scans (Benbow and Bull, 2011). Yanaga et al. propose adapting contrast dose based on body weight in kilograms (Yanaga *et al*., 2007) However, there is no consensus on the most accurate method of adapting contrast doses.

2.6 Conceptual framework

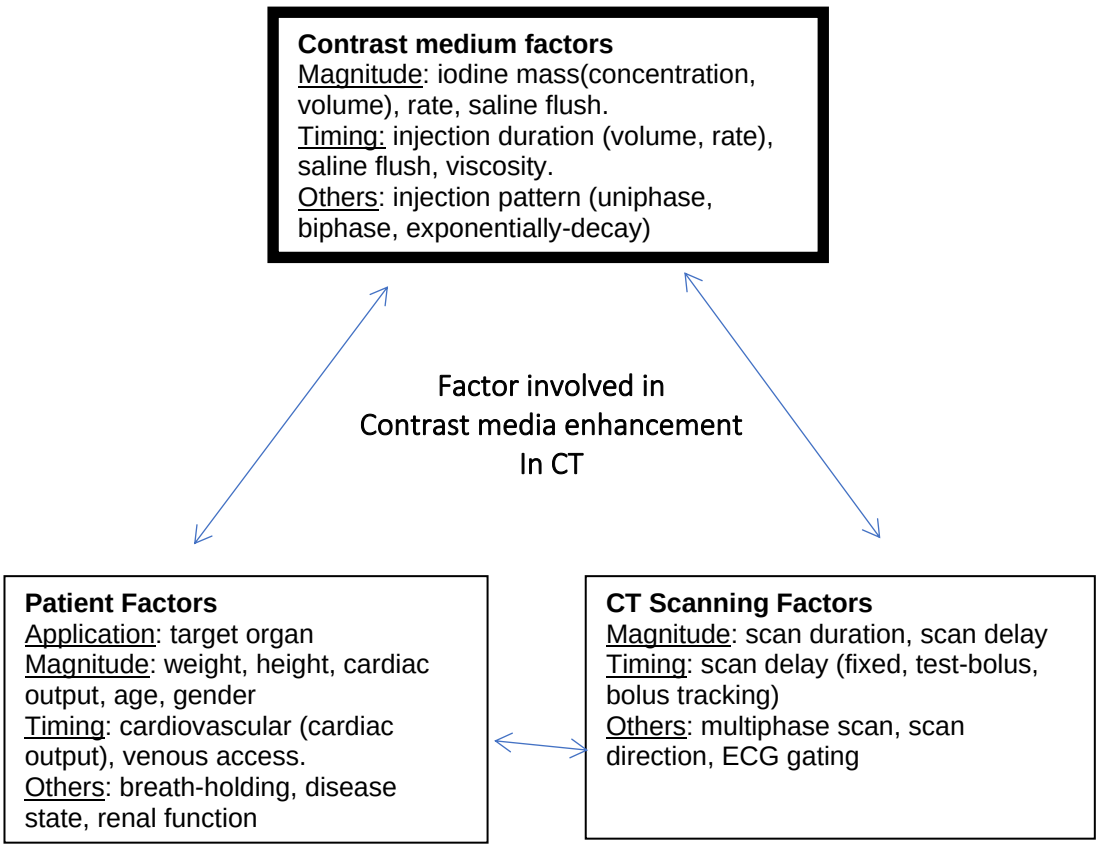

Figure 1 Conceptual framework.

2.7 Rationale of Study

Thus, the aim of this study is to compare the effect of the two different scanning protocols mentioned above on the contrast enhancement and image quality of CECT abdomen and their validity in clinical practice. We hope this study can be used in future as a guideline or reference in standardizing the iodinated contrast material administration protocol in CECT abdomen.

CHAPTER 3: METHODOLOGY

3.1 Study Design

This is a retrospective cross-sectional study which will be conducted at Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan and Advanced Medical and Dental Institute (AMDI), Kepala Batas, Penang. Retrospective data will be obtained from these hospitals from the period of January 1st, 2017 until December 31st, 2019.

3.2 Sample Population

i. Reference population – All patients performing CECT abdomen
ii. Source population – Patients performing CECT abdomen in HUSM and AMDI.
iii. Target population – Patients more than 18 years old with contrasted abdominal CT in HUSM and AMDI.
iv. Sampling frame – Eligible patients according to inclusion and exclusion criteria from the target population.

3.3 Sample Size Calculation

Sample size estimation was calculated based on the previous literature review in 2018 by Perrin E et al. A minimum sample size of 151 samples per group to be able to reject the null hypothesis with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. The independent t-test statistic will be used to evaluate this null hypothesis. With an additional of 10% dropout rate, the sample size is 168 samples per group.

Thus, a minimum total of 168 samples are required to be obtained from AMDI and HUSM respectively, with the total samples of 336.

3.4 Sampling Method

Non-randomized convenience sampling from images of CECT abdomen which were performed from January 2017 until December 2019 as per criteria mentioned.

3.5 Inclusion Criteria

1. CECT abdominal images of adult subjects (age more than 18 years old) which were performed from 2017 until 2019 in HUSM and AMDI.

2. The CECT Abdomen in AMDI is performed based on weight-based contrast volume with bolus tracking technique as stated below.:

- Weight based contrast volume： Iodinated contrast medium 300mg iodine/mL is used, as demonstrated in Table 1. Contrast amount is based on body weight (525mgI/kg).

- Bolus tracking technique: Radio-opaque contrast media is injected into the patient via a peripheral intravenous cannula as per protocol. The volume of contrast is tracked using a region of interest (abbreviated "R.O.I.") at the liver and then followed by the CT scanner once it reaches the level (50 Hounsfield unit). Images are then acquired.

3. The CECT Abdomen in HUSM is performed based on fixed contrast volume with fixed time-delay technique.

- Injection of 100mls IV contrast iodinated contrast media (300 mg/ iodine/mL) with injection rate of 3mls/sec is given, followed by 50 mls saline chaser with injection rate of 3mls/sec.

- Images are acquired after 60 sec delay.

4. CT scan machine and scanning parameters used:

	AMDI	HUSM
Manufacturer	Siemens	Siemens
Scanner model	SOMATOM Definition AS	SOMATOM Definition AS
Year of installation	2015	2009
Slice acquisitions per rotation	128	128
Kilovoltage peak (kVp)	120	120
milliampere (mA)	Variable	Variable

Table 2 CT scan machine and scanning parameters used in two centers**.**

3.6 Exclusion Criteria

1. Patient with abnormality of the aorta or portal vein (to limit anomalies in objective measurement).

2. Patient with heart failure, sepsis or in shock.

3. Patients who underwent CECT Abdomen without standard stipulated protocol.

3.7.1 Research Tools

1. At AMDI:

- Picture Archives Communication System (PACS),

- electronic Radiology Information system (e-RIS)

2. At HUSM:

- Picture Archives Communication System (PACS),
- electronic Radiology Information system (e-RIS)

3.8 Operational Definition

CT	:	Computed Tomography. Medical imaging technique that uses computer-processed combinations of multiple X-ray measurements taken from different angles to produce cross-sectional images of a body.
Hounsfield unit (HU value)	:	Quantitative scale to define radiodensity.
Fixed contrast volume	:	Same amount of contrast medium is used for each patient.
Weight-based contrast volume	:	The amount of contrast medium used is tailored based on patient's body weight.
Automatic bolus tracking	:	Temporal changes of contrast enhancement at a sampling site is measured while contrast medium is injected. When a predefined threshold is reached, CT scan is triggered automatically.
Fixed time-delay	:	A predetermined time interval is set after the beginning of contrast administration. CT scan is triggered after the time interval and is same for every patient.

3.9 Data Collection

Patient Cohort

This is a retrospective cross-sectional study which is be conducted at HUSM and AMDI. This study had obtained approval from the Human Research Ethics Committee of USM (USM/JEPeM/20020126). Retrospective data will be obtained from images of CECT abdomen which have been performed from January 1st, 2017 until December 31st, 2019 at HUSM and AMDI. CT scan images which fulfilled the inclusion criteria will be included. We excluded the patient with aorta or portal vein abnormality, patient with heart failure, sepsis or shock, and patients who underwent CECT Abdomen without standard stipulated protocol.

Computed Tomography (CT)

All CECT scans were performed on Siemens multidetector CT scanner (Somatom Definition AS, Siemens, 128 slices), utilizing a standard 120-kVp setting. Variable milliampere (mA) was utilized according to scan protocol because it does not affect the CT attenuation number. CECT scan of the abdomen in each center was performed according to the standard protocol as mentioned in the inclusion criteria. Axial images were acquired with thin collimation reconstructed with 5.0 mm thickness at 3.0 mm intervals using a standard soft tissue algorithm. The axial CT series were assessed on a standard radiology picture archiving and communication system (PACS) workstation.

Quantitative Assessment

Quantitative assessment was performed using Centricity PACS RA1000, GE Healthcare workstation with images viewed in soft tissue window setting as follow:

- Window width (W) = 450.
- Window level (L) = 50.

For quantitative assessment, the total number of samples will be grouped into two main groups: fixed contrast volume with fixed time-delay protocol and weight-adapted contrast volume with automatic bolus tracking protocol. Objective measurements of the CT attenuation number measured in Hounsfield units (HU) will be collected from each sample at the regions of interest (ROI) placed within the abdominal aorta (25 mm2) and portal vein (25 mm2). All measurements were taken at similar anatomical levels. For the assessment of aortic enhancement, ROI is placed at the level of celiac trunk for aortic enhancement. For the assessment of venous enhancement, ROI is placed at the level of main portal vein.

The data collected will be documented in the data collection sheet. The subject's information will be labelled with serial number to maintain privacy and confidentiality of subject. Data obtained will be calculated by investigator and then validated by a radiologist with more than five years' experience in abdominal CT imaging interpretation. The same radiologist will be reviewing all the images from both centers.

Qualitative measures

For qualitative assessment, an experienced radiologist will perform a subjective assessment of image quality independently using a 4-point scale. (1: poor contrast enhancement, 2: fair contrast enhancement, 3: good contrast enhancement, 4: excellent contrast enhancement). A score will be award to each sample after reviewing the images. Reader will be asked to review entire scan with focus on perceived sharpness/detail of the organ/structure in question, particularly liver and spleen. No duration or time limit is allocated to review each sample. All images will be anonymized, and the radiologists will be blinded to which protocol had been used. This scoring system is based on the previous literature review in 2018 by Perrin E et al.

The score will be documented in the scoring sheet. The data collected will then be regrouped into respective protocols in the data collection sheet.

3.10 Statistical Analysis

All data were analyzed using Statistical Product and Service Solutions (SPSS) for Windows, SPSS Inc.© (Version 24, SPSS Inc., Chicago, IL, USA). First, the data will be manually entered into the software. The data cleaning will be subsequently conducted to detect any errors that could affect the accuracy of the results. After that, the actual analysis will be carried out. In this study, descriptive statistics will be employed for selected variables. The findings will be presented based on the types and distribution of the data. Categorical data will be presented as frequencies and percentages, while numerical data will be presented as means and standard deviations (if normally distributed), or as medians and interquartile ranges (if not normally distributed).

Comparison of the differences in normally distributed numerical data between two independent groups will be analyzed using the independent t-test, while the Mann-Whitney test will be used if the data are not normally distributed. To study the association between two sets of categorical data, Pearson's chi-square test for independence will be used, while Fisher's exact test will be used if the assumptions for the Pearson's chi-square test for independence are violated. All probability values are two-sided, and a level of significance of less than 0.05 (p-value < 0.05) will be considered as statistically significant.

In our study, comparison of numerical data between two independent groups will be applied for both quantitative assessment and qualitative assessment. Hence, both sets of data will be presented as means and standard deviations (if normally distributed), or as medians and interquartile ranges (if not normally distributed). Comparison of the differences in normally distributed numerical data between two independent groups will be analyzed using the independent t-test, while the Mann-Whitney test will be used if the data are not normally distributed**.**

3.11 Confidentiality and Privacy

Subject's names will be kept on a password-protected database and will be linked only with a study identification number for this research. The identification number instead of patient identifiers will be used on subject data sheets. All data will be entered into a computer that is password protected. On completion of study, data in the computer will be copied to CDs and the data in the computer erased. CDs and any hardcopy data will be stored in a locked office of the investigators and maintained for a minimum of three years after the completion of the study. The CDs and data will be destroyed after that period of storage. Subjects will not be allowed to view their personal study data, as the data will be consolidated into a database. Subjects can write to the investigators to request access to study findings.

3.12 Ethical Consideration

The study was approved by Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM code: USM/JEPeM/20020126) which complies with the Declaration of Helsinki (see Appendix).

3.13 Study Flow Chart

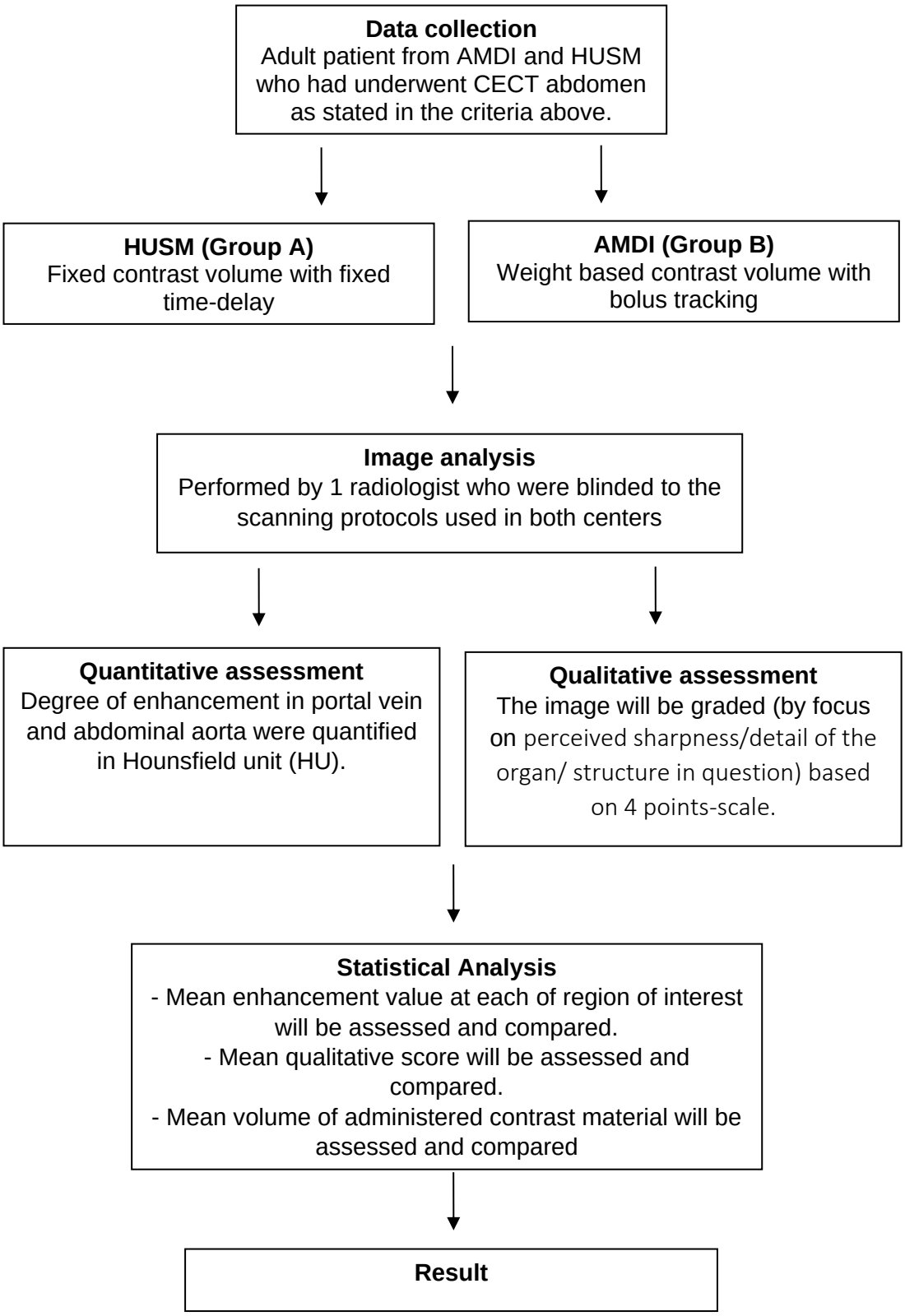

Figure 2 Study flow chart