Studies on Benign Hepatic And Pancreatic Pathology

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A thesis submitted for the degree of

Masters of Philosophy (Surgery)

to

The University of Adelaide

October 2021

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Abstract

Background

Malignant pathologies of hepatic and pancreatic lesions have been widely reported. However, benign pancreatic and hepatic pathologies are infrequently focused on owing to their innocuous nature. The significance of indeterminate liver lesions (ILL) and a novel pancreatic entity - intraductal tubulopapillary neoplasm (ITPN) are explored. With the escalating incidence of obesity, a better understanding of fat distribution, metabolism, and its clinical implications are critical to managing pancreatitis. Visceral adipose tissue (VAT) and sarcopenia are valued as contributors to prognosis and outcomes in these patients.

Objective

The pathologies of ILL and ITPN pose a diagnostic conundrum and have created a management dilemma for clinicians. This thesis examines the characteristics and natural history of these pathologies, and attempt to provide current strategies to aid diagnosis and management. This thesis also focuses on the impact of VAT and sarcopenia in pancreatitis. The main purpose is to highlight the current data available and identify gaps in knowledge surrounding these pathologies.

Design

The four papers contributing to this thesis include a retrospective cohort study, a review and two systematic reviews. The retrospective cohort study consisted of a retrospective analysis of prospectively collected data from a single institution for eight years. The systematic reviews utilised NCBI PubMed, EMBASE as data sources and selected all studies published since 2000.

Results

The results cover an overview of clinical, radiological, histopathological, and molecular features, as well as the prognosis and up to date management of ILL and ITPN. The cohort study concluded that small (<15 mm) hepatic lesions discovered incidentally in patients with no known primary malignancy and risk factors are virtually always benign, with a 1% risk of malignancy. The review on ITPN discovered that the diagnosis of ITPN is invariably made post-operatively and is considered to be a precursor lesion to carcinomas but has a favourable prognosis.

The systematic review on VAT identified 11 studies. Nine studies showed a statistically significant association between VAT and the severity of AP. Four studies found VAT to be a risk factor for acute pancreatitis. Two studies showed VAT is associated with an increased risk of local complications and two other studies showed a correlation between VAT and mortality. The systematic review on sarcopenia in chronic pancreatitis (CP) analysed six studies. The prevalence of sarcopenia in CP from all studies ranged from 17-62%. Sarcopenia was associated with a reduced quality of life, increased hospitalisation, and reduced survival.

Conclusion

This thesis provides the foundation for further work to be undertaken on these surgically challenging diseases. There is a need for a classification system, which stratifies ILLs by malignant potential based on a standardized and evidence-based approach. Further studies are essential to elucidate the natural history of ITPN to guide the best treatment strategy and determine survival. The systematic reviews established that VAT and sarcopenia have significant prognostic values and should be incorporated into prognostic scores of pancreatitis

and future prospective analyses. A multidisciplinary approach in an experienced hepatobiliary and pancreatic centre is recommended for the management of these challenging benign pathologies.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Li Lian Kuan

15/09/2021

Publications arising from this thesis

Four research articles have been published from Chapters 2, 3, 4 and 5 of this thesis.

Kuan LL, Mavilakandy A, Oyebola T, Bhardwaj N, Dennison AR, Garcea G. Indeterminate liver lesions - a virtual epidemic: a cohort study over 8 years. ANZ J Surg. 2020 May;90(5):791-795. doi: 10.1111/ans.15685. Epub 2020 Feb 21. PMID: 32086883. (Impact Factor: 1.9)

Kuan LL, Dennison AR, Garcea G. Intraductal Tubulopapillary Neoplasm of the Pancreas and Bile Duct: A Review. Pancreas. 2020 Apr;49(4):498-502. doi: 10.1097/MPA.0000000000001518. PMID: 32282762. (Impact Factor: 3.3)

Kuan LL, Dennison AR, Garcea G. Association of visceral adipose tissue on the incidence and severity of acute pancreatitis: A systematic review. Pancreatology. 2020 Sep;20(6):1056-1061. doi: 10.1016/j.pan.2020.05.027. Epub 2020 Jun 27. PMID: 32768177. (Impact Factor: 3.6)

Kuan LL, Dennison AR, Garcea G. Prevalence and Impact of Sarcopenia in Chronic Pancreatitis: A Review of the Literature. World J Surg. 2021 Feb;45(2):590-597. doi: 10.1007/s00268-020-05828-0. Epub 2020 Nov 9. PMID: 33165641; PMCID: PMC7773619. (Impact Factor: 2.6)

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Acknowledgements

This thesis would not be possible without the time, support, encouragement and contribution of the various people in my life. I would like to thank the people who contributed in one way or another.

First and foremost, I would like to express my gratitude to my supervisors. I owe my success to Professor Guy Maddern, who gave me purpose and direction for my career path. Thank you for your continuous guidance and support in accomplishing this thesis. Your enthusiasm for research has encouraged me to persist on and pursue the academic road. To Markus Trochsler, who I have the pleasure to work alongside in the unit. Thank you for believing in me, and for all the support and encouragement that you have shown me throughout the years.

To Professor Ashley Dennison, my former mentor, thank you for your immense support, teaching and practical wisdom imparted to me during my time in Leicester. Your knowledge has been invaluable and I will always be grateful for your vast experience. To Professor Giuseppe Garcea, who provided me with a platform to expand on my research skills. I will always be grateful for your wise counsel on matters of life. To Harsh Kanhere, for his utmost support and for cheering me on.

To my co-authors; Taiwo, Akash and Neil who contributed to the data collection in the first publication in this thesis, thank you. To Anna Holasek, thank you for your aid in literature searches.

To my beloved family, thank you for your unwavering support. To Kim Zhuan, you have been my pillar of strength throughout this journey and words cannot describe my appreciation of you.

Chapter 1

Introduction

Chapter 1: Introduction

Malignant pathologies of hepatic and pancreatic diseases have been widely explored and reported. However, benign pancreatic and hepatic pathologies are less frequently focused on owing to their innocuous nature. A greater awareness of these benign pathologies is necessary. This thesis focuses on benign hepatic (indeterminate liver lesions) and pancreatic (intraductal tubulopapillary papillary neoplasm) pathologies as well as the impact of obesity and sarcopenia in pancreatitis, which is the most common benign pancreatic condition. The works submitted into this thesis include a retrospective cohort study, a review and two systematic reviews. The main purpose was to investigate and illustrate the current available evidence surrounding these pathologies. In all the studies, the main aim was to identify investigative methods available to ascertain diagnosis, explore the impact on patient's prognosis and provide up to date management. This thesis highlights the current data available and identifies gaps in knowledge on these pathologies.

1.1 Liver lesions

Lesions in a variety of organs are being increasingly recognized as an incidental finding on high resolution cross-sectional imaging and they can be benign, premalignant or malignant.(1) They constitute an added burden to the health care cost, as multiple subsequent investigations are frequently required to achieve a diagnosis in these patients. The most common primary liver malignancies are hepatocellular carcinoma and intrahepatic cholangiocarcinoma. They have characteristic imaging findings, however a number of benign entities can appear similar and give rise to diagnostic dilemma. The most frequent solid benign lesions of epithelium origin are focal nodular hyperplasia and hepatocellular adenoma; and of mesenchymal origin are haemangioma and angiomyolipoma.(2) Accurate characterization of benign lesions is

pertinent to avoid misdiagnosing them as cancers, which may lead to subsequent unwarranted operation or invasive intervention.(3) An adequate knowledge of the diagnostic and therapeutic approach will impact on the subsequent treatment planning. Two per cent of patients undergoing abdominal ultrasound have sonographically indeterminate liver lesions, of which, seven per cent are malignant.(4) The underlying concern of most clinicians and patients is that these indeterminate lesions may correspond to metastases or primary liver carcinoma.

The first study was undertaken to review the outcome of liver lesions labelled as 'indeterminate' in asymptomatic patients without a biopsy-proven concomitant primary tumour. The secondary aim was to assess the impact on healthcare resources and cost-effectiveness with regards to the frequency and modality of radiological scans, multidisciplinary team discussions and clinic reviews. Currently, there are no established clinical criteria or strategies for managing these nodules. Detection of indeterminate lesions on imaging often generates additional radiology diagnostic testing and/or tissue biopsy to provide definitive diagnosis; which is associated with both patient benefits and harms. Therefore, the objective of this research was to observe the natural course of indeterminate liver lesions detected on radiological imaging and evaluate appropriate management strategies for these lesions. This is presented in chapter two.

1.2 A novel pancreatic lesion

Pancreatic cancer is a heterogeneous, complex and dismal disease to treat. In order to make significant progress against pancreatic cancer, we need to focus our efforts on early detection and not solely on treating metastatic disease.(5) The detection and treatment of early, non-

invasive disease have a major impact on cancer mortality. Analogous to other carcinomas, the current knowledge about pancreatic carcinogenesis postulates a stepwise progression from intraepithelial neoplasia to invasive cancer.(6–8)

Two major precursor lesions to invasive pancreatic carcinoma; pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) have been widely discussed in the literature in the past decade.(9) These neoplasms are considered to be premalignant owing to their common association with and demonstrated progression to invasive carcinoma.(10) Pancreatic intraepithelial neoplasia is defined as a microscopic papillary or flat and non-invasive epithelial neoplasm arising from the pancreatic ductal epithelium. Pancreatic intraepithelial neoplasia is divided into 2 subtypes: low-grade PanIN (previously reported as PanIN-1 and PanIN-2) and high-grade PanIN (previously reported as PanIN-3) involving a carcinoma in situ. (9,11,12) Intraductal papillary mucinous neoplasm of the pancreas is characterized by papillary growths within the pancreatic ductal system with thick mucin secretion, and is at risk for undergoing malignant transformation.(13) It is widely recognized as one of the most common cyst-forming pancreatic neoplasms.

The discovery of a novel entity; intraductal tubulopapillary neoplasm (ITPN) of the pancreas, constitutes a rare subgroup of intraductal epithelial neoplasms of the pancreas has created both excitement but also ambiguity. Intraductal tubulopapillary neoplasm progresses with tubulopapillary growth and was recognised by the World Health Organization in 2010 as a distinct entity.(14) Intraductal tubulopapillary neoplasm is a distinct clinicopathologic entity in the pancreas (15) and contributes to a diagnostic dilemma. Knowledge of the natural history, pathology, and clinical behaviour of ITPN is still deficient and our understanding of the

disease is still evolving. Accordingly, recognition of the difference between ITPN in the pancreas and in the bile duct proves to be challenging. It is fundamental to differentiate ITPN from IPMN as ITPN carries a more favourable prognosis.(16) A review was conducted to expound this entity better. The third chapter discusses on ITPN of the pancreas and bile duct.

1.3 Body composition and pancreatitis

Pancreatitis, a benign pancreatic pathology remains a critical public health problem despite advances in medical technology and new effective treatments.(17) The burden of pancreatitis is increasing, and globally, acute pancreatitis is the most common pancreatic disease whilst pancreatic cancer is the most lethal.(18) The incidence of acute pancreatitis ranges from 13 to 45 per 100,000 population-years and that of chronic pancreatitis ranges from 5 to 12 per 100,000 population-years.(19) Improved awareness of pancreatitis, its risk factors, and treatment are warranted to reduce the future burden of this condition.

With the rising prevalence of obesity, there is a plethora of literature discussing the relationship between obesity and acute pancreatitis as a contributor to a worse prognosis and outcomes in these patients cohort. Obesity is now recognised by the World Health Organization as a global epidemic (20) and represent a rapidly growing threat to the health of population. Obesity poses a unique set of problems for acute pancreatitis. In the past decades, the increase in obesity has been paralleled by an increase in the incidence (21–24) and severity (25–28) of acute pancreatitis. Globally, in 2017, the age-standardized rates for pancreatitis were 76.2 per 100,000 population for the point prevalence, 20.6 per 100,000 population for incidence, and 4.5 per 100,000 population for years lived with disability.(29)

With the escalating incidence of obesity, a better understanding of fat distribution, metabolism, and its clinical implications is critical to managing diseases. Variations in body composition and the assessment of sarcopenia have gained the interest of clinicians in recent years. Different body composition counterparts are being assessed in various patient populations and sarcopenia is valued as a prognostic factor of morbidity and mortality.(30)

Several studies have shown visceral adipose tissue (VAT) to be more accurate in predicting prognosis of acute pancreatits than basal metabolic index (BMI) alone. Visceral adipose tissue is a hormonally active component of total body fat, which possesses unique biochemical characteristics that influence several normal and pathological processes in the human body.(31) Abnormally high deposition of VAT is known as visceral obesity. Visceral obesity is an independent component of metabolic syndrome and the magnitude of obesity directly relates to the prognosis of this condition.(32,33)

There is a paucity of data in regards to VAT and its impact in patients with acute pancreatitis (AP). The knowledge of these implication would contribute to better management of patients with these conditions. The very first systematic review was conducted to investigate this effect of VAT in acute pancreatitis. This is discussed in chapter four.

A body composition of low muscle mass and high fat mass in the presence of decreased muscle strength and/or physical function is known as sarcopenic obesity.(34) Sarcopenia and obesity share common pathophysiologic mechanisms, including lifestyle behaviors, hormones, and immunological factors, all of which may act synergistically to affect the risk of developing a series of adverse health consequences.(35) Sarcopenia is characterized by a relative reduction in lean muscle mass associated with compromised nutritional status and

immunological function, and can be easily measured through preoperative computed tomography.(36) Current available data on the impact of sarcopenia on the prevalence and outcomes in chronic pancreatitis are scarce. As no previous systematic review has been performed, a systematic review of the literature was conducted to investigate this. This is presented in chapter five.

Chapter 2

Indeterminate liver lesions - a virtual epidemic:

A cohort study over 8 years

Chapter 2: Overview

Indeterminate Liver Lesions

This chapter focuses on ILL frequently encountered on imaging in asymptomatic patients. This poses a diagnostic conundrum and has created a management dilemma for clinicians. A study was undertaken to review the outcome of liver lesions labelled as 'indeterminate' in asymptomatic patients without a biopsy-proven concomitant primary tumour. The secondary aim was to assess the impact on healthcare resources and cost-effectiveness with regards to the frequency and modality of radiological scans, multidisciplinary team discussions and clinic reviews.

Kutaiba et al. commented on this paper; “The study highlights the issue of incidental findings and subsequent investigations and costs to healthcare systems. Such an issue is not usually considered when a radiological test is requested and the authors were able to show real-world consequences of such findings.” (37)

This article was also cited in Zhang B, Ratnakanthan P, Shekarforoush M, Clements W. Should we report incidental low-density liver lesions with benign features? A retrospective single centre analysis of trauma CT scans. Journal of Gastrointestinal and Abdominal Radiology. 2020 Oct 22. (38)

Statement of Authorship

Title of Paper	Indeterminate liver lesions - a virtual epidemic: a cohort study over 8 years.
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and ~~Unendorsed~~ work written in manuscript style
Publication Details	~~Kuan~~ LL, ~~Mavilakandy~~ A, ~~Oyebola~~ T, ~~Bhardwaj~~ N, Dennison AR, ~~Garcea~~ G. Indeterminate liver lesions - a virtual epidemic: a cohort study over 8 years. ANZ J Surg. 2020 May;~~90~~(5):791-795. ~~doi~~: 10.1111/ans.15685. ~~Epub~~ 2020 Feb 21. PMID: 32086883.

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Overall percentage (%)	70%
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Signature	Date: 20/9/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

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ii. ~~permission~~ is granted for the candidate in include the publication in the thesis; and

iii. ~~the~~ sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Contributed to the final version of the manuscript. Supervised the project.		
Signature		Date	29/9/21

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Contribution to the Paper	Conceived the original idea. Processed the data and interpretation of the results. Per results and the editing of t the project.		
Signature		Date	29/9/21

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Indeterminate liver lesions – a virtual epidemic: a cohort study over 8 years

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Key words
diagnostic imaging, hepatic, incidental finding, liver, neoplasms.

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Accepted for publication 12 December 2019.

doi: 10.1111/ans.15685

Abstract

Background: Within the last decade, advances and availability in radiological imaging have led to an increase in the detection of incidental liver lesions (ILLs) in the asymptomatic patient population. This poses a diagnostic conundrum. This study was undertaken to review the outcome of liver lesions labelled as 'indeterminate' in asymptomatic patients without a biopsy proven concomitant primary tumour. The secondary aim was to assess the impact on healthcare resources and cost effectiveness with regards to the frequency and modality of radiological scans, multidisciplinary team discussions and clinic reviews.

Methods: The study consisted of a retrospective analysis of prospectively collected data from the University Hospitals of Leicester multidisciplinary team database. The study period ranged from 2010 to 2015. All patients were followed up for 3 years to ensure no late re occurrences with malignancy.

Results: A total of 92 patients with ILL were identified. The median age was 72 years. The median size of these ILLs was 10 mm. Eighty seven patients required supplementary imaging and 42 required a third imaging. Ninety one patients had benign lesions. Only one case was biopsy proven to be malignant.

Conclusion: Small (<15 mm) hepatic lesions discovered incidentally in patients with no known primary malignancy and risk factors are virtually always benign, with a 1% risk of malignancy. There is a need for a classification system, which stratifies ILLs by malignant potential based on a standardized and evidence based approach. This is important to prevent unnecessary investigations. A multidisciplinary approach in an experienced hepatobiliary and pancreatic centre is recommended until such a classification exists.

Introduction

Within the last decades, advances and availability in radiological technologies have led to an increase in the detection of incidental liver lesions (ILLs) in the asymptomatic patient population. This poses a diagnostic conundrum and has created a management dilemma for clinicians. Although most of these lesions are eventually characterized as benign, malignancy has to be ruled out as misclassifications of these lesions have a significant impact. Detection of ILL serves both as an opportunity and a catalyst to exposure of unnecessary risks. Early detection of a harmful lesion may result in life saving, curative procedure; however, in patients with benign disease, it may also subject them to unnecessary cascades of investigations with their own attendant risks. In addition, there is a significant economic burden imposed on health care with investigations and/or treatments.

Despite advances in innovation, there are limitations in characterizing small hepatic lesions (<1 cm) that do not conform to the typical radiological features. These are classified as indeterminate, and often require further investigations with another modality for final characterization.

The workup of 'incidentalomas' has varied widely by clinicians and regions, and some standardization is desirable in light of the current need to limit costs and reduce risk to patients.[1] Strategies for optimal detection and characterization of liver lesions should be developed according to the clinical picture, the likelihood of malignant disease and the presence of underlying diffuse liver disease.[2] Currently, in the absence of biomarkers and evidence based

guidelines, a multidisciplinary approach in an experienced tertiary referral centre is recommended for an optimized individual management.[1]

This study was undertaken to review the outcome of liver lesions labelled as 'indeterminate' in asymptomatic patients without a documented biopsy proven concomitant primary tumour. The sec ondary aim was to assess cost effectiveness in view of frequency and modality of radiological scans, multidisciplinary team (MDT) discussions and clinic reviews.

Methods

This is a retrospective analysis of prospectively collected data from the University Hospitals of Leicester MDT database. The key sea rch term was liver lesions labelled as indeterminate without a biopsy proven concomitant primary tumour. This exclusion param eter was applied after manual review of medical records and MDT minutes. The study period ranged from 2010 to 2015. All patients with ILL discovered incidentally without a clear radiological diag nosis were followed up to the final conclusion of the nature/diagno sis of the lesion(s). All lesions were labelled as indeterminate, 'difficult/too small to characterize' or 'further imaging required' based on their primary imaging modality with subsequent varication at the specialist MDT and reported by a hepatobiliary and pancreatic (HPB) radiologist. ILLs that were characterized with confidence as benign or malignant were excluded from the study. All subsequent surveillance imaging for ILLs was reviewed. All patients were followed up for 3 years to ensure no late re occurrences with malignancy.

Clinical data of the number and modality of scans, risk factors, number of MDT discussions and clinic reviews including virtual clinic reviews were recorded. The MDT consisted of six HPB sur geons, gastroenterologists, radiologist, oncologists, pathologists, a dietitian and three HPB cancer nurse specialists. Patients with a documented biopsy proven concomitant primary malignancy were excluded from the analysis. All local ethical guidelines for retro spective studies in the trust were adhered to.

For the purpose of clarity, in our study, ILL was defined by a preoperative suspicion of a sinister lesion however with inconclu sive initial imaging findings, irrespective of its size. Patients with a known concomitant biopsy proven malignancy were excluded from further analysis as these patients represent a distinctly different cohort (as many may go on to have resection of their primary tumour with 'watchful waiting' of their indeterminate liver lesion or their primary lesion may be unresectable due to local advance ment and hence further investigations for subsequent metastases may not be undertaken).

Results

A total of 92 patients, 51 males and 41 females, with cross sectional or sonographic imaging demonstrating ILL were identi fied. The median age was 72 years (range 43 99 years).

Risk factors

Thirteen percent of patients presenting with ILL have risk factors. They consisted of alcohol/fatty liver 10%, hepatitis cirrhosis 2% (newly diagnosed) and alcohol cirrhosis 1% (newly diagnosed).

Imaging modality

The initial diagnostic imaging modality and subsequent imaging (second and third modalities) are shown in Figure 1. Forty two patients whose diagnoses remained indeterminate following a sec ond imaging modality underwent further imaging. Two patients (5%) required an octreotide scan due to concurrent finding of a lesion in the body of the pancreas, suspicious for neuroendocrine tumour. The time interval between the first and second scan was a median of 4 weeks and between the second and third scan was 6 weeks. Examples of ILLs on imaging are provided in Appen dix S1.

Number and size of ILL, and organs of potential primary tumours

The median size of these ILLs was 10 mm (average 12 mm). Thirty seven patients had a single liver lesion, 22 patients had two liver lesions and 33 patients had three or more liver lesions. The organs of potential primary tumours on initial imaging are depicted in Figure 2.

Final characteristics of ILL

Ninety one patients had benign lesions, and only one patient had a final diagnosis of malignancy. As only one malignant lesion was identified, risk factors for malignancy could not be statistically determined. The final diagnoses are shown in Table 1. 12.1% of ILLs were never characterized; however, surveillance proved them to be benign. 7.7% of lesions were not seen with subsequent imag ing. Two patients underwent a liver biopsy for confirmation of diagnosis and one had histology confirming adenocarcinoma.

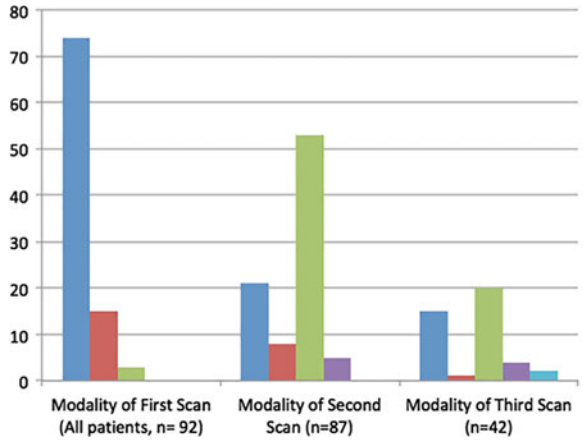

Fig. 1. Modality of imaging in the first, second and third scans. ■, Computed tomography; ■, ultrasound; ■, magnetic resonance imaging; ■, positron emission tomography; ■, octreotide.

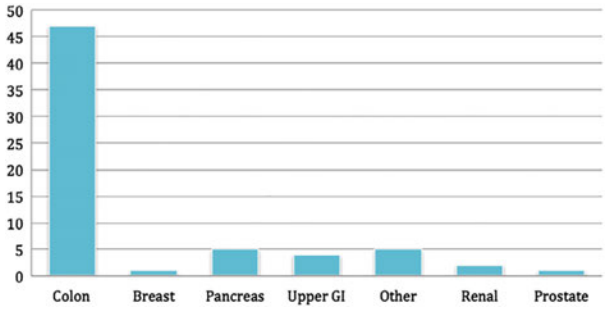

Fig. 2. Organs of potential primary tumours on initial imaging.

Number of MDT discussions and clinic appointments

The median number of weeks on the MDT discussions was four, with an average of 12. The median number of times a patient was presented in the MDT was two. 5.4% of patients were signed back onto the MDT for further discussion after being signed off from it. The total number of MDT discussions for all patients was 180, the number of clinic appointments was 60 and the number of virtual clinic reviews was 56.

Costings

The cost assessing these patients was derived via two methods. Imaging costs were initially based on the UK nationally agreed tar iffs. However, for most National Health Service service providers, the tariff costs per scan do not reflect the true cost of any interven tion, as additional activity such as sub contracting to external pro viders (to manage diagnostic targets) and additional pay for consultant staff and allied healthcare professionals for 'out of work ing time' clinical activity are not factored in. To understand the true cost of delivering scans and out patient activity, the Patient Level Information and Costing System (PLICS) was used (Table 2).

Discussion

Despite advances in radiological technology, incidental ILLs remain a diagnostic challenge. Demographic factors may play a crucial role in aiding the diagnosis of ILLs as sensitive and specific biomarkers are unavailable. Established risk factors for hepatocellu lar carcinoma (HCC), for example, are hepatitis B and C virus infections, alcohol induced liver disease and non alcoholic fatty liver disease.[2] Hence, an ILL in the context of this condition may require more vigorous evaluation or follow up. However, the over all incidence of HCCs in patients without cirrhosis is difficult to estimate and varies with region and the prevalence of risk factors in the population.[3]

Low risk patients are those with no known primary malignancy, hepatic dysfunction or hepatic risk factors.[4] Our population study is comprised of a majority of low risk patients with only 13% of risk factors; 3% with liver cirrhosis. A degree of pre test probability should be applied to the patient's age, gender, risk factors, history of malignancy, clinical presentation, previous imaging and labora tory findings and whether knowledge of a specific diagnosis would alter management.[5] Large multicentre cohort studies are probably needed to obtain this level of information, which can be used to develop risk stratification algorithms to better determine individual risk.

The accurate characterization of a liver lesion ultimately lies in the diagnostic quality imaging. Patients who are referred from dis trict hospitals often have suboptimal imaging. An ultrasound (USS) performed by a sonographer instead of a consultant radiologist may differ, as it is operator dependent. Also, a computed tomography/ magnetic resonance imaging (CT/MRI) scan performed may not be of standardized imaging protocol, that is, contrast administration rate, type of contrast, phase/timing of scan, thickness of axial images and attenuation correction. This may well require repeat imaging with appropriate contrast phases to accurately characterize an ILL.

The unenhanced CT phase should be eliminated whenever possi ble, as it does not provide additional information in many cases.[4] A reduced dose contrast enhanced CT demonstrates inferior diagnos tic performance for detecting low contrast liver lesions.[6] Sub optimal quality imaging adds to the diagnostic dilemma, and if a diagnosis is not achieved during the MDT, these patients are sub jected to either a repeat of the same imaging modality of optimal/ higher quality or another modality to aid in characterizing the lesion.

Table 2 Distribution of cost across MDT discussions, clinic reviews and imaging

	Cost based on PLICS	Tarif based cost
MDT discussions	£14 539†	
Clinics	£425 917	‡
Radiology scans	£453 236	£54 025

†£81 per patient. ‡Unable to derive accurate data between new, follow up, general surgery or specialist clinic consultations; therefore, only PLICS data were used. MDT, multidisciplinary team; PLICS, Patient Level Information and Costing System.

Table 1 Final characteristics of indeterminate liver lesions eventually ruled as benign

	Cyst	Complex cyst	Haemangioma	Never characterized	No lesion seen	Adenoma	FNH	Vascular artefact	Regenerative nodule
n	47	2	18	11	7	2	2	1	1
%	51.6	2.2	19.8	12.1	7.7	2.2	2.2	1.1	1.1

FNH, focal nodular hyperplasia.

The experience of the radiologists and interobserver variability plays a part in the diagnosis of HCC as it is primarily made by subjective analysis by radiologists on the basis of enhancement patterns.[7] Our MDT consists of experienced and consistent radiologists with a special interest in HPB hence providing expert interpretation of these lesions. Lesion detection and characterization were improved in subsequent scans following sonographic localization of the ILL due to the added value of a previous USS resulting in an improved detection rate of 66% for all sizes of lesions studied.[8] The diagnosis of most liver lesions can be determined due to their typical imaging characteristics and especially when taken in conjunction with the patient's demographics.[5]

In our study, at least two dynamic studies (USS, CT or MRI) were used for each patient prior to achieving a diagnosis. USS is a non invasive test and more readily accessible. In our study, USS only accounts for 16% as a primary imaging modality. It is a good diagnostic and surveillance tool; however, the main limitation of USS is the detection of small tumours (<2 cm).[9] Other variables such as lesion location, body habitus and sonographic technical factors have to be accounted for and most indeterminate lesions larger than 5 mm on CT can be detected and characterized on hepatic sonography.[8]

CT is the most frequent initial modality for which these ILLs are discovered in our study. Interestingly, MRI was the preferred choice as a second modality (56%). MRI is frequently used as a problem solving technique for the evaluation of focal hepatic lesions that are deemed indeterminate with other imaging modalities.[10] Adopting a policy where MRI is used as the primary cross sectional imaging modality of choice on sonographic or CT detected ILLs may improve characterization rates. Albeit a dearer option, if a diagnosis can be achieved quickly with it without subjecting the patient to another modality and alleviating their anxiety, a justification could be made here.

In some equivocal cases where imaging is insufficient to provide a diagnosis, liver biopsy is commonly used when such knowledge would affect subsequent management decisions.[4] However, the risks of potential complications such as major haemorrhage, bile leak, seeding of tumour, injury to bowel/lung, infection and pain need to be outweighed. It has a morbidity of 0.5% and a mortality of 0.05%.[11] Silva *et al*. in a systematic review have shown that the incidence of needle tract tumour seeding following biopsy of a HCC is 2.7% overall or 0.9% per year.[12]

The American College of Radiology Committee on Incidental Findings presented recommendations for managing liver lesions that are incidentally detected on CT. They proposed that in low risk patients with incidental hepatic lesion <1 cm, generally, no further workup is required and can be considered benign unless the lesion has suspicious features. In incidental hepatic lesions ≥1 cm and with suspicious features, a further workup with MRI or biopsy is required. In high risk patients with incidental hepatic lesions >1 cm, MRI is advised in 3 6 months for surveillance.[4]

It can be concluded that small (<15 mm) lesions discovered incidentally in patients with no known primary malignancy are virtually always benign.[13,14] As shown in our study, 99% of ILLs with the median size of 10 mm were benign. The calculated prevalence of benign focal liver lesions shows that on the incidental discovery of liver lesions, first consideration should be given to focal fatty sparing, simple hepatic cysts and haemangiomas.[15] The most commonly encountered benign hepatic lesions fall into four major categories: hepatic cysts, perfusional changes, haemangiomas and focal nodular hyperplasia.[16]

One question to ponder on is whether surgical resection should be performed in cases of incidental ILLs, when malignancy cannot be fully ruled out preoperatively on imaging and biopsy. This study has shown that there is a risk of malignancy in 1% of low risk patients with ILLs. Some centres advocate liver resection; however, there is a mortality rate of 1.6 7% for all liver resections.[17 22] Hence, we assume that for every liver resection performed for ILLs, the number of death outweighs the benefit in order to save 1% of this patient population.

A stepwise and standardized diagnostic approach to ILLs at a multidisciplinary HPB centre is necessary. Consideration should be given to a selective approach on which imaging modality of choice should be used after the first scan in order to achieve a diagnosis quickly as conducting all three imaging modalities on all patients is not feasible, and would result in treatment delays and an increase in financial cost.

Our study also attempted to elucidate clinicopathological variables that could assist in predicting malignancy in ILLs; however, due to only a single lesion proving to be malignant, no statistically significant conclusion can be drawn from this. A classification system that further stratifies ILLs by malignant potential can assist clinicians in determining an optimal treatment plan and is associated with a high negative predictive value.[23]

Some caution needs to be applied in interpreting the economic cost associated with the assessment of ILLs. For example, the costs associated with MDT discussion would not be reduced by eliminating discussion of these lesions, as these costs are built into MDTs, and the MDT framework would still require being in place even if no ILLs were discussed. Other costs, such as clinic discussions and additional imaging, could be reduced by modifying the assessment pathway. Again, this would require robust evidence to ensure that potentially treatable cancers are not missed as a result. Attaching a monetary value to the workup of these patients is useful in that it neatly describes the time and personnel resources attached to ILLs. In particular, it correlates with the 'noise' created by ILLs within an already pressured healthcare system, which in turn may prejudice the evaluation of actual HPB malignancies.

The present study has several significant limitations because of the retrospective design and the small sample size. An algorithm was not formulated due to the low number of actual malignant diseases. Large, multicentre, prospective studies are needed to investigate the best approach of this clinical conundrum. Clinicopathological variables will help identify patient population with higher risk factors of a malignant diagnosis. This will eventually allow the development of evidence based diagnostic and therapeutic treatment.

Conclusion

Small (<15 mm) hepatic lesions discovered incidentally in patients with no known primary malignancy and risk factors are virtually

always benign, with a 1% risk of malignancy. There is a need for a classification system, which stratifies ILLs by malignant potential based on a standardized and evidence based approach. This is important to prevent unnecessary investigations. A multi disciplinary approach in an experienced HPB centre is rec ommended until such a classification exists.

Conflicts of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online ver sion of this article at the publisher's web site:

Appendix S1: Examples of incidental liver lesions.

Chapter 3

Intraductal tubulopapillary neoplasm of the pancreas and bile duct.

Chapter 3: Overview

Intraductal Tubulopapillary Neoplasm of the Pancreas and Bile Duct.

This chapter discusses ITPN of the pancreas and bile duct, which are novel entities. Similarly to the previous chapter, the advancement of high-resolution technology and widespread use of radiological imaging have led to the identification of an increasing number of patients with asymptomatic, non-inflammatory cystic lesions of the pancreas.(39) It is unclear on how to best manage patients with this diagnosis because little is known about its progression to cancer. However, these neoplasms are considered to be precursor lesions to carcinomas but have a favourable prognosis. A review was conduct to provide an update on the current knowledge of ITPN of the pancreas and bile duct with an overview of clinical, radiological, histopathological, and molecular features, as well as the prognosis and management**.** This chapter sets out to explore the more uncommon diagnosis of this benign pancreatic lesion.

This article was cited in Huang X, You S, Ding G, Liu X, Wang J, Gao Y et al. Sites of Distant Metastases and Cancer-Specific Survival in Intraductal Papillary Mucinous Neoplasm With Associated Invasive Carcinoma: A Study of 1,178 Patients. *Front Oncol*. 2021;11:681961.(40)

Statement of Authorship

Title of Paper	Intraductal Tubulopapillary Neoplasm of the Pancreas and Bile Duct: A Review.
Publication Status	[Published] Accepted for Publication Submitted for Publication Unpublished and Unsubmitted work written in manuscript style
Publication Details	**Kuan LL**, Dennison AR, Garcea G. Intraductal Tubulopapillary Neoplasm of the Pancreas and Bile Duct: A Review. Pancreas. 2020 Apr;49(4):498-502. doi: 10.1097/MPA.0000000000001518. PMID: 32282762.

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Name of Principal Author (Candidate)	Li Lian Kuan
Contribution to the Paper	Performed the systematic review. Performed the data collection and analysis of the results. Performed the writing and editing of the manuscript.
Overall percentage (%)	80%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date: 20/9/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co author contributions is equal to 100% less the candidate's stated contribution.

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Signature	Date: 29/9/21.

Intraductal Tubulopapillary Neoplasm of the Pancreas and Bile Duct

A Review

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Abstract: Intraductal tubulopapillary neoplasms (ITPNs) of the pancreas and bile duct are contemporary entities. It is unclear on how to best manage patients with this diagnosis because little is known about its progression to cancer. This review provides an update on the current knowledge of ITPN of the pancreas and bile duct with an overview of clinical, radiological, histopathological, and molecular features, as well as the prognosis and management. Embase and Medline databases search were performed to identify studies that evaluated ITPN of the pancreas and bile duct. The infrequent exposure to this variant poses a diagnostic challenge. The diagnosis of ITPN is almost always made postoperatively because there are no characteristics on radiological studies to distinguish it from other cystic neoplasms of the pancreas. As ITPN has a favorable prognosis, it is crucial to establish an accurate diagnosis and differentiate it from other pancreatic and biliary variants. These neoplasms are considered to be precursor lesions to carcinomas, hence, surgery and close clinical surveillance are recommended. Further studies are essential to elucidate the natural history of ITPN, guide best treatment strategy and determine disease recurrence and survival.

Key Words: cystic tumors of pancreas, cystic tumors of bile duct, intraductal tubulopapillary neoplasm, carcinoma of pancreas, carcinoma of bile duct, cholangiocarcinoma

(*Pancreas* 2020;49: 498 502)

The advancement of high resolution technology and wide spread use of computed tomography (CT) and ultrasound have led to the identification of an increasing number of patients with asymptomatic, noninflammatory, cystic lesions of the pan creas.[1] Two major precursor lesions to invasive pancreatic carci noma; pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) have been widely discussed in the literature in the past decade.[2]

The discovery of a novel entity, intraductal tubulopapillary neoplasm (ITPN) of the pancreas, constitutes a rare subgroup of intraductal epithelial neoplasms of the pancreas and has created both excitement and ambiguity. It was first recognized by the Japanese investigators, and in 2002, the Japan Pancreas Society proposed the name intraductal tubular carcinoma.[3,4] This was renamed in 2009 to ITPN. Intraductal tubulopapillary neoplasm also affects the bile duct. This biliary counterpart is known as ITPN of the bile ducts (ITPN b). Yamaguchi et al[4] found that all the features of ITPN were distinct from those of other known intraductal pancreatic neoplasms, including PanIN, IPMN, and the intraductal variant of acinar cell carcinoma.

Pancreatic intraepithelial neoplasia is a common precursor lesion of pancreatic ductal adenocarcinoma (PDAC). They are mi croscopic papillary or flat, noninvasive epithelial neoplasms that are usually less than 5 mm and confined to pancreatic ducts[5] (hence they are too small to be seen by radiologic imaging or grossly). They are composed of columnar to cuboidal cells with variable mucin and are divided into 3 grades according to degree of cytological and architectural atypia.[5]

Intraductal papillary mucinous neoplasm is defined as a macroscopically visible, predominantly papillary (or rarely flat), noninvasive, mucin producing epithelial neoplasm arising in the main pancreatic duct or branch ducts.[6] They can be classi fied as main duct, branch duct, or mixed type based on their site of origin and extent of tumor. Radiologically, the charac teristic feature is a cystic mass like appearance, either single or multiple, depending on its location, with communication to the main pancreatic duct or its branches.[7] These features help to distinguish these tumors from mucinous cystadenoma/ cystadenocarcinoma.[7] Excessive mucin production by the neoplastic cells results in cystic dilatation of the pancreatic duct and, possibly, spillage of mucin from the ampulla of Vater, a classic (but not uniform) finding at endoscopic retro grade cholangiopancreatography (ERCP).[8]

Mucinous cyst neoplasm can be differentiated from IPMN by the presence of ovarian type of stroma and by the absence of communication with the ducts.[9] In 2010, the World Health Organization recognized ITPN of the pancreas as a distinct en tity, which was included in the subgroup of premalignant epi thelial tumors of the pancreas. It was defined as intraductal, grossly visible, tubule forming epithelial neoplasm with high grade dysplasia, and ductal differentiation without overt pro duction of mucin.[10]

Intraductal tubulopapillary neoplasm of the pancreas is a rare primary pancreatic neoplasm accounting for less than 1% of all pan creatic exocrine neoplasms and 3% of intraductal neoplasms of the pancreas.[11] These neoplasms are considered to be premalignant owing to their common association with, and demonstrated progres sion to invasive carcinoma.[12] They can be either cystic or solid mass forming, and morphologically, can mimic some subtypes of IPMN. The incidence and oncologic outcomes of ITPN are unknown due to its rarity, however, it has been shown to have a better prognosis than IPMN.[13,14]

The infrequent exposure to this variant poses a diagnostic challenge. This review provides an update on the current knowl edge of ITPN of the pancreas and bile duct with an overview of clinical, radiological, histopathological, and molecular features, as well as the prognosis and management.

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DOI: 10.1097/MPA.0000000000001518

MATERIALS AND METHODS

A comprehensive search of the scientific literature was performed using Embase and Medline databases to identify all studies, which evaluated ITPN of the pancreas and bile duct. The following search terms were used: "pancreas", "pancreatic", "bile duct", "intraductal tubulopapillary neoplasm", "ITPN", "histology", "immunohistochemistry", "follow up", "surveillance", "natural history", "natural course", "cancer", "malignant" and "carcinoma." No date limits were set. The search was restricted to English language studies (Fig. 1).

RESULTS

All relevant articles on cases of ITPN of the pancreas and bile duct were reviewed. The clinical presentations, radiological findings, histopathology features, differential diagnoses, molecular characteristics, and treatment options are discussed below.

Clinical Presentation

Intraductal tubulopapillary neoplasm of the pancreas (ITPN p) has an even sex distribution and an average age of presentation at 56 years old.[4,13] No risk factor has yet been elucidated. Two thirds of patients present with a variety of nonspecific symptoms, which include abdominal pain, jaundice, diarrhea, or weight loss.[14] The remaining are asymptomatic, with the discovery of tumors being an incidental finding on imaging studies. In one of the largest case series, Basturk et al[15] identified no specific disease related symptoms in 18 (54.5%) of 33 patients. It can also present as acute pancreatitis. Five cases have been reported in the literature, hence, it is important to bear in mind of the possibility of ITPN after the diagnosis of idiopathic acute pancreatitis.[16] Due to the low incidence of ITPN p, its diagnosis is often delayed and confirmation of diagnosis is usually made postresection, as clinical and radiological findings are often nonspecific.

Intraductal tubulopapillary neoplasm mainly occurs in the head of the pancreas, but it can also involve the body or tail and in some cases the entire pancreas. Tumors were most frequently located in the head of pancreas (52%), body (17%), tail (7%), both the head and body (3%), both the body and tail (7%), and in the whole pancreas (14%).[17] The tumor has a mean size of 3 cm[17] and median size of 4.5 cm.[15]

Preoperative diagnosis of ITPN p is challenging as there are no specific laboratory tests, or characteristics on imaging studies to discriminate it from other cystic neoplasms of the pancreas. The diagnosis is usually confirmed postresection after exhaustive immunohistochemical staining. Furthermore, there are limitations on imaging to differentiate ITPN from IPMN.

Interestingly, there is also a biliary counterpart of pancreatic ITPN, but data on it is still limited due to the small number of reported cases. Schlitter et al[18] conducted a multicenter study of 20 cases of biliary ITPNs and they were seen in patients in their 60s (mean, 62 years). The tumors were found located in the regions of: intrahepatic (70%), extrahepatic (10%), and perihilar (20%).[18] The mean tumor size was 6.9 cm.[18] However, these tumors can range in size from 0.6 to 8.0 cm.[19] Associated invasive carcinomas were present in 80% of cases, and were mainly conventional tubular adenocarcinomas (50%).[18] Most of the invasive adenocarcinomas showed either focally or predominantly, a tubular pattern, undifferentiated from ordinary cholangiocarcinomas.[18]

This neoplasm has also been identified in the gallbladder as a subset under the heading of intracholecystic papillary tubular neoplasm. They are relatively indolent neoplasia with significantly better prognosis compared with pancreatobiliary type gallbladder carcinomas.[20]

RADIOLOGY

Radiographic modalities, including contrast enhanced CT, magnetic resonance (MR) imaging including MR cholangiopancreatography, ERCP, and endoscopic ultrasonography (EUS), are often utilized preoperatively to aid with the diagnosis and management. Intraductal tubulopapillary neoplasm of the pancreas demonstrates a dilated and irregular main pancreatic duct, but without an abundance of low attenuation mucin.[21] Motosugi and Yamaguchi[22] described the characteristic imaging findings as the 2 tone duct sign on CT/MR and the cork of wine bottle

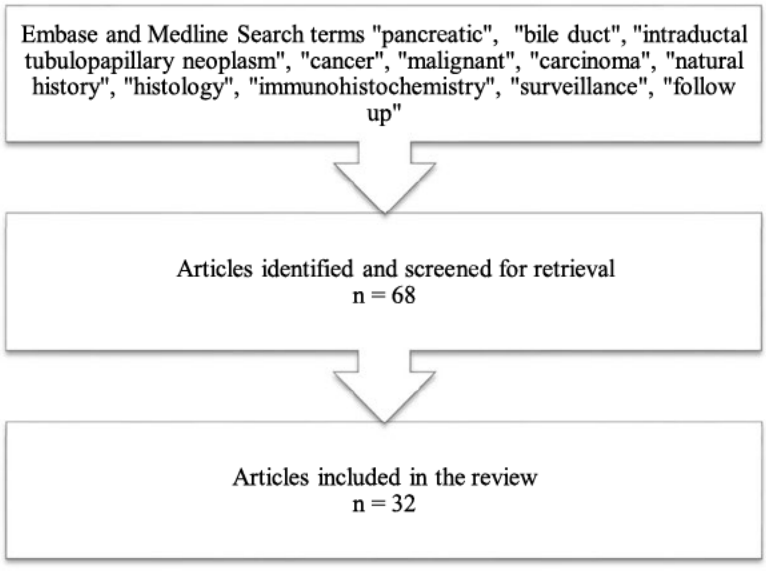

FIGURE 1. Methods of the scientific literature search.

sign on MR cholangiopancreatography/ERCP that represent their intraductal growth. Low signal intensities on T1 weighted and high signal intensities on T2 weighted MR im ages; and dilatation of the pancreatic duct and atrophy of the pancreatic parenchyma in the tail region are frequently seen on contrast enhanced CT.[22]

Endoscopic ultrasonography guided fine needle aspiration has been used to diagnose ITPN by cytological immunohistochemistry.[23] Large cribriform and tubular clusters with luminal spaces con taining wispy mucin were considered to be diagnostic clues for the ITPN.[23] Tajima[24] recognized the diagnostic value of EUS guided fine needle aspiration and described the diagnostic fea tures of ITPN which are tubules in contact with fibrovascular structures, and this correlated well with the histological find ings of the postoperative specimen. Despite the advances in im aging modalities, ITPN can only be diagnosed postoperatively due to its ambiguity on imaging. This resembles to the diagno sis of PanIN.

HISTOPATHOLOGY

The main characteristics of ITPN p are the appearance of a solid nodular tumor obstructing dilated ducts on macro scopic examination, no visible secreted mucin, tubulopapillary growth, uniform high grade atypia throughout the neoplasm, easily recognizable necrotic foci, and ductal differentiation.[4] They grow in a predominantly tubular pattern with minimal papilla formation.[25] The nodular masses are usually large, dense, and fleshy to rubbery with the surrounding pancreatic parenchyma exhibiting acinar atrophy with stromal fibrosis[10] (Table 1). Associated invasive carcinoma has been reported in 45.4% of cases.[4]

In 2010, Park et al[28] reported the first case of ITPN b, a bil iary carcinoma resembling ITPN p with tubulopapillary growth. All biliary ITPNs were characterized by large, smooth contoured nodules composed of prominent, relatively small, back to back tubular units.[18] Necrosis was common (85%), predominantly focal (40%), and with "comedocarcinoma like pattern" (40%).[28] Zen et al[26] observed that the associated biliary cysts were peribiliary cysts partly lined by carcinoma cells that were continuous with the intracystic papillotubular masses and with pathological and genetic features similar to those of ITPN p.

TABLE 1. Histopathological, Immunohistochemical, and Molecular Characteristics Differences Between ITPN and IPMN[4,9,12,14,15,17 19,25 27,29]

	Intraductal Tubulopapillary Neoplasm	Intraductal Papillary Mucinous Neoplasm
Atypia	Uniform, high-grade dysplasia	Low- to high-grade dysplasia
Mucin	No	Yes
Tubule forming	Yes	No
MUC1	Positive	Negative Positive (pancreatobiliary type)
MUC2	Negative	Positive (intestinal type)
MUC5AC	Negative	Positive
Trypsin	Negative	Negative
Fascin	Negative	Positive
KRAS mutations	Rare (10%) (wild type)	More common (40% 60%)
BRAF mutations	Rare	More common

IMMUNOHISTOCHEMISTRY

Intraductal tubulopapillary neoplasm of the pancreas is often compared with IPMN for its similar characteristics. They are both intraductal and have the ability to become invasive. Hence, immu nohistochemical studies play a crucial role in determining the ductal differentiation of pancreatic neoplasms. The immunohistochemical features of ITPN p include testing positive for MUC1, cytokeratin 7 (CK7), and/or cytokeratin 19 (CK19), and negative for trypsin, MUC2, MUC5AC, and fascin.[4,14] Kolby et al[17] reported that im munohistochemical staining was positive for CK7 in 100% of the patients, CK19 in 95% and MUC1 in 88%. Trypsin was negative in all cases, β catenin was negative in 94%, and MUC2 was nega tive in 96% of the cases.[17] The Ki 67 labelling index showed vari able expression between 6% and 43%[17] and were significantly associated with invasion.[4]

Immunohistochemically, ITPN b has similar characteristics to ITPN p.[27] They are characterized by the expression of MUC1 (80%) and MUC6 (30%) and by the absence of MUC2 and MUC5AC.[18] Katabi et al[19] reported that the tumor cells expressed CK19, carbohydrate antigen (CA) 19 9, MUC1, and MUC6 in most cases, whereas MUC2, MUC5AC, synaptophysin, chromogranin, and CA 125 were negative in all cases.

MOLECULAR FEATURES

There are limited studies regarding molecular profile of ITPN p. *KRAS* mutations are more commonly observed in IPMN and PDAC, but has been reported in only 10% of cases in ITPN.[29] Molec ular genetics reveal *KRAS*, *GNAS*, and *RNF43* as the most frequently mutated genes in IPMNs, whereas ITPNs show wild type *KRAS*.[30] Mutations of *PIK3CA* is more frequently found in ITPN than in IPMN and PDAC.[29] However, BRAF and p53 mutations were in frequently seen.[17] The SMAD4 expression was retained in 100% of cases, p16 expression and p53 overexpression were seen in 33% and 27% of cases, respectively.[15]

The molecular alterations observed in ITPN b included *CDKN2A/p16* (intraductal components 44%, invasive 33%) and TP53 (intraductal components 17%, invasive 9%).[19] Mutations in *KRAS* (intraductal 6%, invasive 0%), *PIK3CA* (intraductal 6%, invasive 0%), and loss of SMAD4/DPC4 (intraductal 7%, invasive 0%) were rare.[19] No mutations were identified in *IDH1/2*, *BRAF*, *GNAS*, EGFR, HER2, and β catenin.[26] Genetic analysis of *KRAS* and *BRAF* revealed wild type genotypes.[26]

DISCUSSION

Although ITPN p has different clinicopathological features to other cystic neoplasms of the pancreas, the treatment strategy for patients with ITPN is similar.[14] To date, there are paucity of reports on ITPN and little is known about its malignant transformation potential and prognosis. Fundamentally, surgical resection follow ing oncologic criteria is recommended to prevent malignant trans formation; however, more data are required to assess adequate treatment and follow up standard.[31] Moreover, surgical resection is often required to establish the definitive diagnosis and to ame liorate symptoms. Pylorus preserving pancreaticoduodenectomy is the most commonly performed therapeutic procedure for ITPN in a curative attempt.[17] Total pancreatectomy and distal pancrea tectomy were performed in several other cases.[17]

The prognosis of ITPN associated invasive carcinoma is better than that of traditional PDAC, even in patients with recurrent and

metastatic disease.[29] As it is less aggressive, it is vital to distinguish it from both IPMN and PDAC.[32] Approximately 40% of ITPN p are associated with invasive carcinoma and high grade cytologic atypia of the tumor cells.[10] A higher risk of invasive growth is as sociated with large tumor size, male sex, increased mitosis and a high Ki 67 proliferative index.[4,17] The invasive component is however limited in extent, and this may account for its more favorable prognosis.[10]

As this is a relatively new entity, there are limited long term data available in the literature. The largest case series by Basturk et al[15] of 33 patients of which 22 patients were followed up for a median period of 45 months, reported the overall postoperative survival rate as 100% in patients without an invasive component and 1 , 3 , and 5 year survival rates of 100%, 91%, and 71% re spectively in patients with an invasive component.[15] A systematic review by Date et al[14] of 58 patients, published the overall postop erative 1 , 3 , and 5 year survival rates of ITPN p as 97.3%, 80.7%, and 80.7%, respectively.[14] Biliary ITPNs also display a fa vorable prognosis with an overall combined survival rates of 100% at 1 year, 90% at 3 years and 90% at 5 years.[18]

The scarcity of cases has yielded limited long term data on survival, and therefore, the management strategies at present in clude a greater awareness of this diagnosis, surgical resection and close clinical surveillance to detect early recurrence. These may then aid in a deeper understanding of the natural history of this disease and its subsequent long term outcomes. No conclu sion about the efficacy of surveillance and follow up programs can be drawn from the current available evidence.

CONCLUSIONS

Intraductal tubulopapillary neoplasms of the pancreas and bile duct are rare entities that make their diagnoses challenging. The diagnosis of ITPN is often always made postoperatively. It is crucial to establish an accurate diagnosis and differentiate it from other pancreatic and biliary variants as ITPN has a more favor able prognosis. As these neoplasms are considered to be precursor lesions to carcinomas, surgery and close clinical surveillance are recommended. Further studies are essential to elucidate the natural history of ITPN, guide best treatment strategy, and determine dis ease recurrence and survival.

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Chapter 4

Association of visceral adipose tissue on the incidence and severity of acute pancreatitis: A systematic review

Chapter 4: Overview

This chapter explores the relationship between VAT and acute pancreatitis. In 2016, an estimated 671 million adults had obesity.(41) The expanding global obesity epidemic has enhanced interest in adipose tissue biology. Evidence has shown a possible correlation between VAT and the incidence and severity of acute pancreatitis. Body mass index (BMI) measurements do not distinguish between truncal and visceral obesity, whereas anatomical fat distribution is thought to be significant as it gives rise to distinct metabolic effects.(42) Particular attention has been directed to VAT, which is characterised as increased adipose tissue surrounding the intra-abdominal organs.(31) This is the first systematic review conducted to establish the relationship between VAT and acute pancreatitis.

This article was cited in Boyle JM, McCall KL, Nichols SD, Piper BJ. Declines and pronounced regional disparities in meperidine use in the United States. *Pharmacol Res Perspect*. 2021;9(4):e00809. (43)

Statement of Authorship

Title of Paper	Association of visceral adipose tissue on the incidence and severity of acute pancreatitis: A systematic review.
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	**Kuan LL**, Dennison AR, Garcea G. Association of visceral adipose tissue on the incidence and severity of acute pancreatitis: A systematic review. Pancreatology. 2020 Sep;20(6):1056-1061. doi: 10.1016/j.pan.2020.05.027. Epub 2020 Jun 27. PMID: 32768177.

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Name of Principal Author (Candidate)	Li Lian Kuan
Contribution to the Paper	Performed the systematic review. Performed the data collection and analysis of the results. Performed the writing and editing of the manuscript.
Overall percentage (%)	80%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date: 20/9/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature	Date: 29/9/21

Pancreatology 20 (2020) 1056–1061

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Association of visceral adipose tissue on the incidence and severity of acute pancreatitis: A systematic review

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ARTICLE INFO

Article history:
Received 31 January 2020
Received in revised form
11 May 2020
Accepted 11 May 2020
Available online 27 June 2020

Keywords:
Visceral fat
Visceral obesity
BMI
Acute pancreatitis
Severe pancreatitis

ABSTRACT

Background: With the rising prevalence of obesity, there is a plethora of literature discussing the relationship between obesity and acute pancreatitis (AP). Evidence has shown a possible correlation between visceral adipose tissue (VAT) and AP incidence and severity. This systematic review explores these associations.

Methods: Eligible articles were searched and retrieved using Medline and Embase databases. Clinical studies evaluating the impact of VAT as a risk factor for AP and the association of the severity of AP and VAT were included.

Results: Eleven studies, with a total of 2529 individuals were reviewed. Nine studies showed a statistically significant association between VAT and the severity of AP. Only four studies found VAT to be a risk factor for acute pancreatitis. Two studies showed VAT to be associated with an increased risk of local complications and two studies showed a correlation between VAT and mortality.

Conclusion: This is the first systematic review conducted to study the association between VAT and AP. The existing body of evidence demonstrates that VAT has a clinically relevant impact and is an important prognostic indicator of the severity of AP. However, it has not shown to be an independent risk factor to the risk of developing AP. The impact of VAT on the course and outcome of AP needs to be profoundly explored to confirm these findings which may fuel earlier management and better define the prognosis of patients with AP. VAT may need to be incorporated into prognostic scores of AP to improve accuracy.

Introduction

Obesity is now recognised by the World Health Organization as a global epidemic [1]. With the escalating incidence of obesity, a better understanding of fat distribution, metabolism, and its clinical implications are critical to managing the disease. Published data prior to the year 2000 did not demonstrate an independent association between obesity and mortality from acute pancreatitis (AP) [2]. In the past decades however, the increase in obesity has been paralleled by an increase in the incidence [3–5] and severity of AP [6–9].

Multiple large prospective, population based studies and meta analyses have demonstrated that obesity (as measured by the Body Mass Index [BMI]) is an independent predictor of severity and mortality from AP [4,8–12]. BMI measurements do not distinguish between truncal and visceral obesity, whereas anatomical fat distribution is thought to be significant as it gives rise to distinct metabolic effects. Particular attention has been directed to visceral adipose tissue (VAT), which is characterised as increased adipose tissue surrounding the intra abdominal organs [13]. VAT is a hormonally active component of total body fat, which possesses unique biochemical characteristics that influence several normal and pathological processes in the human body, and is associated with globally worse outcomes and metabolic disturbances [13].

Several prediction models and risk scores have been proposed to anticipate the severity and prognosis of patients with AP; however, their clinical utility are variable and do not take obesity into consideration [14]. The possible explanation for the relationship between visceral obesity and severe AP is that VAT leads to a chronic pro inflammatory state which may predispose patients to mount a greater inflammatory response once AP occurs [15]. Several studies have shown VAT to be more accurate in predicting

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https://doi.org/10.1016/j.pan.2020.05.027
1424-3903/

prognosis of AP than BMI alone.

AP typically resolves in the majority of patients without further complications, but 20% of patients progress to severe AP (defined by organ failure persisting beyond 48 hours) with a resultant much higher mortality rate (up to 30%) [16]. Evidence has shown a possible correlation between VAT and AP incidence and severity. This systematic review explores these associations.

Methods and materials

A search was performed using PubMed and EMBASE databases to identify all studies, which evaluated the association of VAT and AP. This review was performed in accordance to the PRISMA guidelines. The following search terms were used: “visceral fat”, “visceral obesity”, “visceral adipose tissue”, “acute pancreatitis”, “risk factor”, “severity”, “complications”. A systematic review of studies published from January 2000 to September 2019 was performed. Due to the paucity of data, conference abstracts were included. The search was restricted to human subjects and English language studies.

The inclusion criteria were; age greater than 18 years, AP defined in accordance to the Atlanta Classification, visceral fat defined and measured with computed tomography (CT) examination, severity of AP defined, and end points of risk factor and/or severity. Potentially relevant studies were identified by title and abstract. Full papers were obtained and assessed in detail. A specifically designed data form was used to collect all relevant data. Two researchers carried out data collection and analysis independently. A third reviewer resolved any discrepancies found by the first two reviewers. The primary outcomes of the review were to evaluate the impact of VAT as an independent risk factor for developing AP and the association of the severity of AP.

Results

A systematic search yielded 73 items, which were screened by title and abstract. Eleven studies met the predetermined eligibility criteria. The selection process of studies included in the review is outlined in Fig. 1 (PRISMA diagram). Eleven studies, with a total of 2529 individuals were reviewed (Table 1). Most studies were retrospective, single centre studies except for one multicentre trial by Sternby et al. [17] which involved six European countries.

Measurements of VAT were obtained byCT examination in the axial plane of either the third, fourth or fifth lumbar vertebrae (L3/L4/L5) or at the level of the L3/L4 intervertebral discs space. Measurements from one study were acquired from an axial CT slice at the level of the centermost point of the L1 vertebra [23]. The regions of interest were drawn by a segmentation software and the cross sectional area of the VAT calculated. The severity of AP was measured using the Atlanta Classification or revised Atlanta Classification [16]. In one of the studies, Madico et al. used hospital length of stay as an indicator of severity [18] (Table 2).

The presence of higher VAT was associated with a significantly increased risk of AP in four studies [19 22]. However, in five studies VAT was not found to be an independent risk factor for AP [17,23 26]. Two studies did not measure VAT as a risk factor for AP [18,27] (Table 2).

Nine of the studies showed a strong association of an increased VAT and the severity of AP [17 23,25,27]. Of these, Ji et al. (in a study of 235 patients with moderately severe or severe AP) demonstrated this finding in a cohort of patients who had hyperlipidaemia acute pancreatitis [22]. Sternby et al. [17] and Jin et al. [25] demonstrated this on univariate analysis with p values of 0.04 and 0.003 respectively. This is shown in Table 3.

A few studies reported a significant association between VAT volume and the subsequent development of local and systemic complications of severe AP. Natu et al. found that an increased VAT area was also associated with a higher incidence of persistent systemic inflammatory response syndrome (SIRS), acute necrotic collections, and multi system organ failure (MSOF) [20]. Yashima et al. found that the presence of a pancreatic pseudocyst was strongly related to VAT volume ($p < 0.001$) in the Japanese population [19]. O'Leary et al. demonstrated an association between VAT, severity, and systemic complications ($p = 0.003$) in a group of 62 patients [23]. O'Leary et al. [23] also showed a strong association between mortality and VAT volume ($p = 0.019$), Xie et al. [21] showed a similar finding ($p < 0.001$) (Table 3).

Discussion

This is the first systematic review performed to investigate the impact of VAT on the risk and severity in AP. The available evidence do not demonstrate an increased VAT to be an independent risk factor for AP. There does however appear to be a strong association between increased VAT and the severity of AP. Numerous other studies have demonstrated that waist circumference, but not BMI, was associated with a statistically significant increase in the risk of AP [28]. A dose dependent relationship showed that a one cm increase in waist circumference was associated with a 16% increase in the risk of severe AP (OR 1.16, 95%CI: 1.1 1.3) [15].

Abdominal obesity is linked to a spectrum of metabolic disorders [29]. In patients with AP, it is postulated that a state of chronic inflammation may have a crucial role in the pathogenesis of obesity related metabolic dysfunction [30,31]. Several mechanisms may explain these results. Intra pancreatic fat and VAT are both metabolically active and predispose to a pro inflammatory state via increased inflammatory mediators such as interleukin (IL) 6 and tumor necrosis factor α (TNF α) as well as reduced levels of adiponectin (which has an anti inflammatory function) [32,33]. Adiponectin regulates the inflammatory response by inhibiting macrophage production of TNF α and IL 6: key cytokines implicated in the severity of AP [29,34]. This pro inflammatory response leads to increase levels of C reactive protein (CRP) and/or the pro inflammatory cytokines (IL 1β, 6 and 8) [8,35]. It is known that the level of adiponectin is inversely associated with abdominal adiposity [36].

The severity of AP is worsened by unregulated lipolysis of visceral fat enriched in unsaturated triglyceride, thus releasing unsaturated fatty acids, which inhibit mitochondrial complexes, causing further necrosis in the setting of necrotizing pancreatitis [37]. Ji et al. conducted a study evaluating the relationship of VAT and the severity of AP induced by hyperlipidaemia [22]. Among the potential mechanisms of hypertriglyceridemia induced pancreatitis, the insolubility of the lipid triglycerides in the aqueous environment of blood resulting in microthrombi is speculated to play role. This leads to stasis in the pancreatic vasculature causing ischemia and pancreatic infarction [37].

Singh et al. studied ectopic fat and abdominal adiposity phenotypes in individuals after AP and concluded that individuals with the presence of diabetes after AP have significantly higher intra pancreatic fat percentage and visceral fat volume compared with individuals without diabetes [38]. CRP levels during hospitalization for AP and biliary aetiology of AP are associated with significantly greater visceral fat and pancreatic fat depots, respectively [38].

Many isolated predictive scoring systems to assess severity of AP have been developed. The result of this systematic review suggests a correlation between VAT and the severity of AP. VAT could be used as an additional predictor in clinical models aimed at predicting the severity of pancreatitis. Further studies are required before VAT measures can be used to improve the prediction of disease severity.

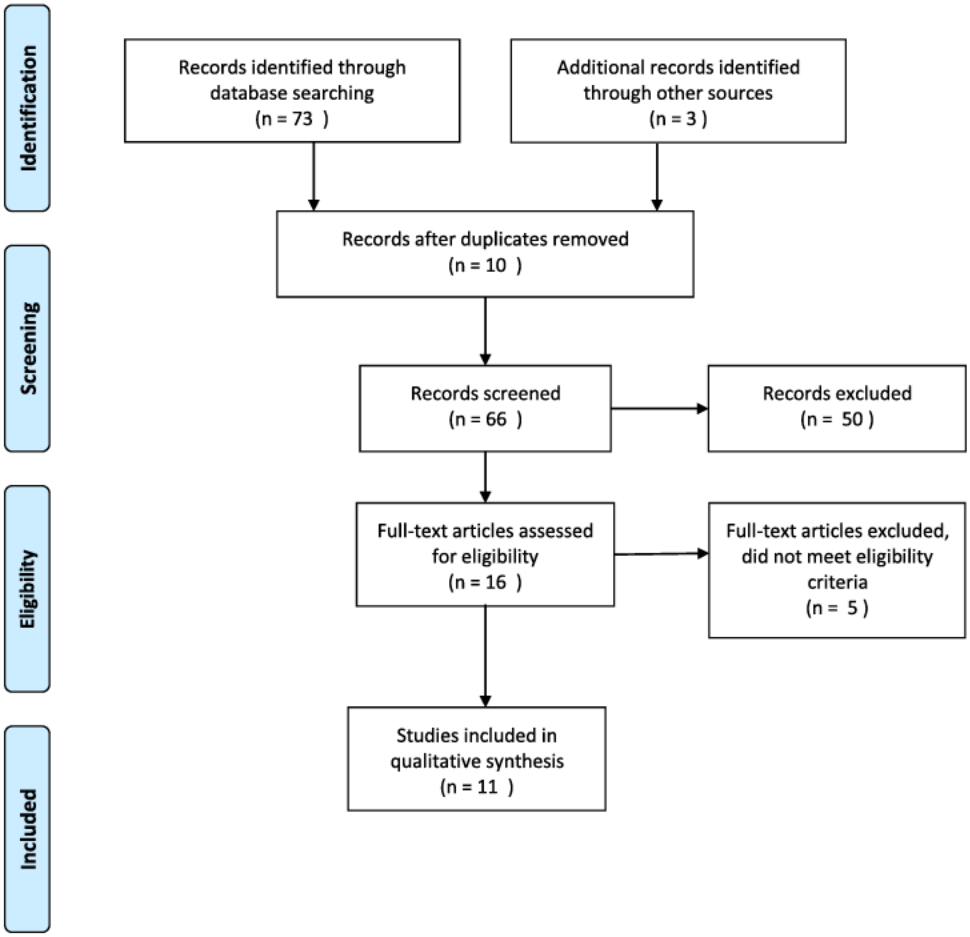

Fig. 1. PRISMA flow diagram on visceral adipose tissue and acute pancreatits.

Table 1
Studies examining VAT as a predictor of AP incidence and severity.

Study	Title	Year	Study type	Location	Population size
Yashima et al.	A large volume of visceral adipose tissue leads to severe acute pancreatitis.	2011	Retrospective, single institution	Tokyo, Japan	124
O'Leary et al.	Effects of abdominal fat distribution parameters on severity of acute pancreatitis	2012	Retrospective, single institution	Cork, Ireland	62
Hall et al.	Is abdominal fat distribution measured by axial CT imaging an indicator of complications and mortality in acute pancreatitis?	2015	Retrospective, single institution	Leicester, UK	79
Natu et al.	Visceral adiposity predicts severity of acute pancreatitis	2017	Retrospective, single institution	Cleveland, Ohio, USA	252
Yoon et al.	Impact of body fat and muscle distribution on severity of acute pancreatitis	2017	Retrospective, single institution	Seoul, South Korea	203
Jin et al.	Risk factors of worsening of acute pancreatitis in patients admitted with mild acute pancreatitis	2017	Retrospective, single institution	Zhejiang, China	602
Imanta Ozola-Zalite et al.	Impact of body composition, measured by CT scan, on acute pancreatitis course	2018	Retrospective, single institution	Riga, Latvia	100
Ji et al.	Evaluation of the severity of hyperlipidaemia pancreatitis using CT-measured visceral adipose tissue	2019	Retrospective, single institution	Nanjing, China	235
Xie et al.	Impact of visceral adiposity on severity of acute pancreatitis: a propensity score-matched analysis	2019	Case-control study single institution	Ningbo, China	306
Madico et al.	Intra peritoneal abdominal fat area measured from computed tomography is an independent factor of severe acute pancreatitis	2019	Retrospective, single institution	Poitiers, France	112
Sternby et al.	Mean muscle attenuation correlates with severe acute pancreatitis unlike visceral adipose tissue and subcutaneous adipose tissue	2019	Multicentre, retrospective trial	European multicentre cohort (involving six centres)	454

Table 2
Characteristics of studies on VAT on the incidence and severity of AP.

Study	Measurement of VAT on CT	Mean BMI ± SD, (kg/m^2)	Median VAT (cm^2)	Number or patients with severe AP N (%)	Measurement of AP
Yashima et al.	L2,L3	23.2 ± 3.9	Mean ± SD :149.5 ± 10.0 (severe) 102.2 ± 6.09 (mild)	48 (38.7%)	Atlanta classification
O'Leary et al.	L1	31.8 ± 7.3	Mean± SD :3.9 ± 2.8	20 (32%)	Atlanta classification
Hall et al.	L2,L3	Median: 24	N/A	5 (6.3%)	Revised Atlanta Classification
Natu et al.	L2,L3 (males) L3, L4 (females)	28.8	103.3	37 (15%)	Revised Atlanta Classification
Yoon et al.	L3	25.7 ± 4.1	150 ± 59	13 (6.4%)	Revised Atlanta Classification
Jin et al.	L3,L4	N/A categorised as BMI >25	N/A categorised as VAT >100	74 (12.3%)	Revised Atlanta Classification
Imanta Ozola-Zalite et al.	L3	27.54	173.6	17 (17%)	Revised Atlanta Classification
Ji et al.	N/A	23.8 ± 3.0	146.7 ± 28.6	37 (15.7%)	Revised Atlanta Classification
Xie et al.	L3,L4	24.4 ± 4.5	136.1 ± 27.3	46 (15.0%)	Revised Atlanta Classification
Madico et al.	L4,L5	26.3 ± 6.9	129.3 ± 68.6 (severe) 100.1 ± 68.4 (mild)	55 (49.1%)	Mild AP: hospital stay up to 5 days Severe AP: hospital stay greater than 5 days.
Sternby et al.	L3	27.7 (24.8 31.1)	171.1 (females) 252.6 (males)	66 (14.5%)	Revised Atlanta Classification

Table 3
Results of studies on the outcomes of VAT on the incidence and severity of AP.[a,b]

Study	Outcomes	Risk factor for AP	Severity of AP	Local Complications	Systemic Complications	Mortality
Yashima et al.	Trend test analysis based on VAT revealed that severity (p 0.01) and local complication (p 0.006) showed significant differences. The presence of a pancreatic pseudocyst was strongly related to VAT volume ($p < 0.001$).	Yes	Yes ($p < 0.001$)	Yes ($p < 0.001$)	Yes (p 0.01)	N/A
O'Leary et al.	VAT volume had the most significant association with severe AP (p 0.003). Strong association between mortality and VAT volume (p 0.019).	No	Yes (p 0.003)	N/A	Yes (p 0.003)	Yes (p 0.019)
Hall et al.	No relationship between fat distribution and either severity of, or mortality from AP. Fat distribution was not found to be an independent risk factor on multivariate analysis. Intra-abdominal fat had the strongest correlation with BMI ($p < 0.0001$).	No	No	N/A	No	No
Natu et al.	VAT area was significantly larger in subjects with severe pancreatitis than in those with mild or moderate disease. (p 0.006) Increased VAT area is a strong predictor of severe pancreatitis, necrosis (p 0.003), and multisystem organ failure (p 0.004).	Yes	Yes (p 0.006)	Yes (p 0.003)	Yes (p 0.004)	N/A
Yoon et al.	Visceral fat-to-muscle ratio demonstrated the highest area under the ROC* curve [0.757, (95% confidence interval: 0.689 0.825)] in predicting moderately severe or severe AP.	N/A	Yes	N/A	Yes	N/A
Jin et al.	BMI ≥25 kg/m^2 (p 0.005) was an independent risk factor for developing more severe pancreatitis. VAT was not a risk factor. Univariate logistic regression analyses indicated that there were significant differences between patients who developed moderately severe AP or severe AP and those who did not in VFA^ (>100 cm2). (p 0.003).	No	Yes on *univariate* analysis (p 0.003)	N/A	Yes (p 0.003)	N/A
Imanta Ozola-Zalite et al.	No significant effect of visceral fat depots on severe acute pancreatitis	No	No	N/A	N/A	N/A
Ji et al.	For patients with moderately severe to severe hyperlipidaemia AP(HLAP), VAT was correlated with BMI and triglycerides (TGs). Significant differences were observed in VAT, total adipose tissue, and triglycerides (TGs) between the HLAP group and the non-HLAP group ($P < 0.001$). VAT and its distribution had no significant effects on mortality.	Yes in *hyperlipidaemia* acute pancreatitis	Yes in *hyperlipidaemia* acute pancreatitis	No	No	No
Xie et al.	VAT is a strong predictor of severity, mortality, and systemic complications in AP. Significant association between AP severity and individual fat parameters. High VAT is an independent negative prognostic indicator of AP.	Yes	Yes ($p < 0.001$)	N/A	Yes	Yes ($p < 0.001$)
Madico et al.	At multivariate analysis, only VAT surface either measured at the umbilical or at the L4-L5 level was associated with AP severity (p 0.017 and 0.006, respectively).	N/A	Yes on *multivariate* analysis (p 0.0006)	N/A	Yes	N/A
Sternby et al.	Correlation of VAT with severity in univariate (p 0.04) but not in multivariate analysis (p 0.07)	No	Yes on *univariate* analysis (p 0.04)	N/A	Yes	N/A

[a] *ROC receiver operating characteristic.
[b] ^VFA visceral fat area.

Interestingly, most studies failed to demonstrate any association on the impact of VAT as an independent risk factor for AP except for four studies. Further research is required to assess if an association exists. At present, no definite conclusions can be made.

It should be noted that some of these studies were performed before the Revised Atlanta Classification [16] was introduced and hence the original Atlanta Classification was used instead. There are important prognostic distinctions between local complications and persistent organ failure that are lacking in the original system as well as the definition of severity. The new classification system for the severity of AP provides an improved and more precise method on the reporting of studies.

Clinically expedient measures for quantifying VAT often lack precision. Umbilical waist circumference has an excellent correla tion with the total abdominal fat area on CT [15]. Borkan et al., in 1982 first reported CT measurement of abdominal adipose tissue [39]. The area at the level of the L3 L4 intervertebral disc was chosen for fat measurement on CT scans because it is a site that reliably assesses the amount of intra abdominal fat, including part of the metabolically active greater omentum [40,41]. Although all of the studies used almost similar axial planes for VAT measurement, they were analysed using different software programmes which is further confounding factor. Specific ranges of Hounsfield units (HU) are the basic radiographic measure used to decipher between different tissues; the window width defining fat tissue varies from 250 HU to 30 HU [42].

The present review included studies which involved a hetero geneous population of patients from South East Asia, Europe, and North America. Other potential confounding factors are the retro spective design of all the studies, rendering the statistical power of analysis weak and prone to bias.

Another limitation is that the timing of CT scans were not synchronised and were performed at varying time points. It is likely that performing a CT scan on a patient within 24 hours of admission with AP, is not common practice in some institutions. In some studies, a CT scan was performed in patients who required it for diagnosis, for suspicion of complications or in the evaluation of the severely ill patients. The inclusion of only patients who underwent a CT scan creates a selection bias toward more severe cases. The underlying area of VAT may have been obscured by subcutaneous and intra abdominal oedema, which is often present in patients with severe AP. This may have led to an underestimation of mea surements of quantity of fat distribution, and an underestimation of its association with outcomes.

Another possible limitation could be from the lack of uniform definition on the severity of AP. One study [18] had definitions of AP severity which did not adhere to the original or revised Atlanta Classification. However, due to paucity of full text studies, the authors felt that this study was relevant and was included. The studies prior to the revised Atlanta Classification use the original version [19,23]. There is also the potential for confounding factors such as comor bidities related to obesity associated metabolic syndrome, which were not routinely evaluated and may have an impact on outcome.

Conclusion

This is the first systematic review conducted to study the as sociation between VAT and AP. The existing body of evidence demonstrates that VAT has a clinically relevant impact and is an important prognostic indicator to the severity of AP. However, it has not shown to be an independent risk factor to the development of AP. The impact of VAT on the course and outcome of AP needs to be profoundly explored to confirm these findings which may fuel earlier management and better define the prognosis of patients with AP.

Funding source

None.

Declaration of competing interest

None.

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Chapter 5

Prevalence and Impact of Sarcopenia in Chronic Pancreatitis: A Review of the Literature

Chapter 5: Overview

This chapter supplements the previous chapter on VAT in the incidence and severity of acute pancreatitis. Chapter five discusses that another vital factor such as muscle mass, like visceral adipose tissue contributes to the holistic management of patients with pancreatitis. Variations in body composition and the assessment of sarcopenia have gained the interest of clinicians in recent years. Sarcopenic obesity is defined as a reduction in lean body mass in the context of excess fat (44) and it is easily overlooked in obese patients. There has been more awareness and interest in sarcopenia of late due to its adverse influence on outcomes.(45–47) This is a first review to examine the prevalence and impact of sarcopenia in patients with chronic pancreatitis (CP).

This article was cited in Furbetta N, Comandatore A, Gianardi D, Palmeri M, Di Franco G, Guadagni S, et al. Perioperative Nutritional Aspects in Total Pancreatectomy: A Comprehensive Review of the Literature. Nutrients. 2021; 13(6):1765.(48)

Statement of Authorship

Title of Paper	Prevalence and Impact of Sarcopenia in Chronic Pancreatitis: A Reviewof the Literature.
Publication Status	Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Kuan LL, Dennison AR, Garcea G. Prevalence and Impact of Sarcopenia in Chronic Pancreatitis: A Review of the Literature. World J Surg. 2021 Feb;45(2):590-597. doi: 10.1007/s00268-020-05828-0. Epub 2020 Nov 9. PMID: 33165641; PMCID: PMC7773619.

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Contribution to the Paper	Performed the systematic review. Performed the data collection and analysis of the results. Performed the writing and editing of the manuscript.
Overall percentage (%)	80%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date: 20/9/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature	Date: 29/9/21

World J Surg (2021) 45:590 597
https://doi.org/10.1007/s00268 020 05828 0

SCIENTIFIC REVIEW

Prevalence and Impact of Sarcopenia in Chronic Pancreatitis: A Review of the Literature

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Accepted: 11 October 2020 / Published online: 9 November 2020

Abstract

Introduction Malnutrition is a common sequela of chronic pancreatitis (CP). Alterations in body composition and the assessment of sarcopenia have gained the interest of clinicians in recent years. There is a scarcity of data currently available concerning sarcopenia in patients with CP. This review aims to investigate the prevalence and impact of sarcopenia in CP.

Methods Embase and Medline databases were used to identify all studies that evaluated sarcopenia and outcomes in patients with chronic pancreatitis. Due to paucity of data, conference abstracts were included. PRISMA guidelines for systematic reviews were followed.

Results Six studies, with a total of 450 individuals were reviewed. Three full text studies and three conference abstracts met the predetermined eligibility criteria. The prevalence of sarcopenia in CP from all studies ranged from 17 62%. Pancreatic exocrine insufficiency was associated as an independent and significant risk factor for sar copenia. Sarcopenia was found to be associated with a reduced quality of life, increased hospitalisation, and reduced survival. It was associated with significantly lower islet yield following total pancreatectomy with islet auto trans plantation in CP.

Conclusion The review of these existing studies amalgamates the limited data on sarcopenia and its impact on CP. It has shown that sarcopenia is exceedingly prevalent and an important risk factor in CP patients. The data presented emphasises that sarcopenia has a significant prognostic value and should be included in future prospective analyses in the outcomes of CP.

Introduction

Malnutrition is a common sequela of chronic pancreati tis (CP). Variations in body composition and the assess ment of sarcopenia have gained the interest of clinicians in recent years. Different body composition counterparts are being assessed in various patient populations and sar copenia is valued as a prognostic factor of morbidity and mortality. Sarcopenia is defined by low levels of measures of muscle strength, muscle quantity/quality and physical performance as an indicator of severity [1]. Sarcopenia is correlated with an increased risk of negative consequences such as physical disability, poor quality of life and death [2 4]. There has been more awareness and interest in sar copenia of late due to its adverse influence on outcomes [5 7]. 'Primary' sarcopenia is defined as the loss in muscle mass and muscle strength when no other cause is evident but ageing itself [2, 8]. 'Secondary' sarcopenia is defined

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as the loss of muscle mass and muscle strength that accompanies underlying chronic diseases, advanced malignancies and malnutrition [2, 9, 10]. Sarcopenia and serum albumin levels are reported to be intimately linked with pancreatic exocrine insufficiency (PEI) in patients with CP [11].

Chronic pancreatitis occurs when repeated episodes of inflammation results in the replacement of pancreatic par enchyma with fibrotic connective tissue [12 14]. The recognised hallmark of advanced CP includes atrophy and fibrosis of the pancreas, distortion of ductal anatomy, strictures, and calcifications, which can result in impair ment of both endocrine and exocrine functions [15, 16].

The quantification of muscle attenuation in clinical practice is a developing field of interest. Current available data on the impact of sarcopenia on the prevalence and outcomes in CP are scarce with only a handful of studies reporting on sarcopenia in pancreatic ductal adenocarci noma (PDAC). We performed a review of the literature to investigate the prevalence and the impact of sarcopenia in patients with CP.

Methods

Medline and EMBASE databases search was performed to identify studies, which evaluated the association of sar copenia and CP. Medical Subjects Headings (MeSH) terms used include: 'sarcopenia', 'chronic pancreatitis', 'ex ocrine pancreatic insufficiency', 'prevalence', 'outcomes', and 'mortality'. The search duration performed was from January 2010 to December 2019. The search was restricted to English language studies. PRISMA guidelines for reviews were followed.

Eligibility criteria included adults over 18 years, studies detailing method of measurement of sarcopenia in CP, prevalence of sarcopenia detected in patients with CP, and outcomes of sarcopenia in patients with CP. The out comes included any impact on CP reported, i.e. any mor bidity or mortality related. The exclusion criteria were studies that did not report on the method of measurement of sarcopenia.

All relevant studies were screened by the title and abstract. All available full text studies were assessed in detailed. The reference lists were reviewed to identify additional appropriate articles. Due to the limited number of available studies on this topic, conference abstracts were included in the review. Two researchers carried out data collection, assessed the risk of bias and analysis indepen dently. Any disagreements were resolved through discus sion between the two reviewers or further adjudication by a third reviewer. The Newcastle Ottawa Quality Assessment Scale was used for the assessment of the quality of the studies. The primary aims of the review were to identify the prevalence and impact of sarcopenia in patients with CP.

Data collection

The data design of each study was retrieved with a pre defined protocol for data extraction. The data captured included relevant information on key study characteristics, patient demographic profile, method of measuring sar copenia, prevalence, and clinical outcomes (any). The intention was to analyse any similarities in negative out comes between the studies, however, the heterogeneity of the findings precluded this.

Results

The search produced 25 studies, and they were identified by title and abstract. After duplicates were removed, 15 studies were screened. Nine studies did not meet the eli gibility criteria and were excluded. Three full text studies and three conference abstracts fulfilled the eligibility cri teria. The PRISMA diagram (Fig. 1) outlines the selection process. Six studies, which comprised of a total population of 450 patients, were reviewed (Table 1). There were two retrospective studies [17, 18] and four [11, 19 21] prospective studies. All studies were performed in a single institution. The studies reported heterogeneous outcomes and these are reported separately below. The outcome variations may well be the reality of clinical practice, but they made comparisons difficult.

Definition of CP and measurement of sarcopenia

A diagnosis of CP was included as defined by the M ANNHEIM classification system [22] in the study by Olesen et al. [19]. The other studies did not report how CP was assessed. Measurement of sarcopenia was performed in five studies at the level of the third lumbar vertebra (*L3*) using computed tomography (CT). The total cross sec tional areas of numerous muscles were quantified, which included the transversus abdominis, external and internal oblique abdominal muscles, rectus abdominis, psoas, erector spinae, and quadratus lumborum. A validated software tool was used for body composition analysis. The study by Olesen et al. measured sarcopenia with anthro pometrics and bioelectric impedance (muscle mass), hand grip (muscle strength), and 'up and go' test (muscle func tion) [19]. The results on the measurement, prevalence, body mass index (BMI), and muscle mass index of sar copenia in patients with chronic pancreatitis are shown in Table 2.

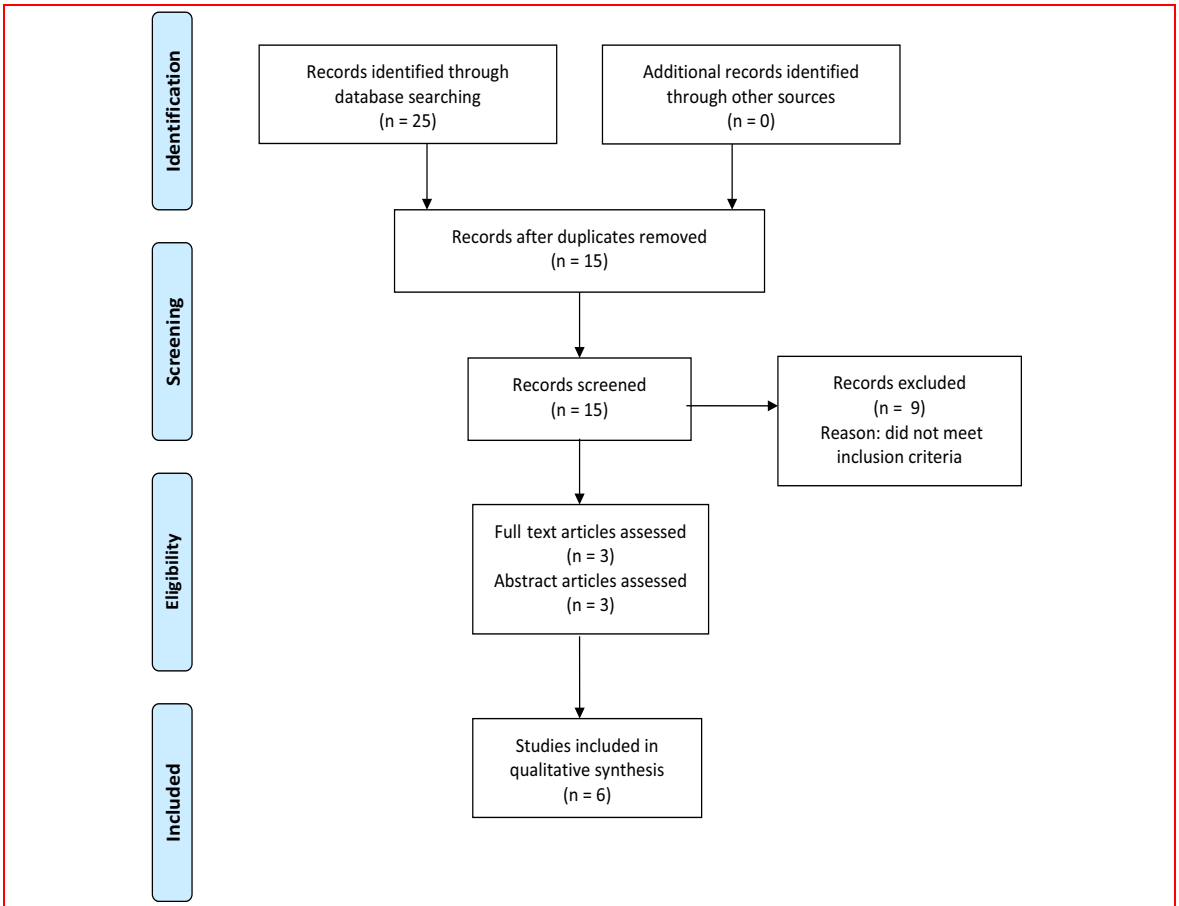

Fig. 1 PRISMA flow diagram on Sarcopenia and Chronic Pancreatitis

Pancreatic exocrine insufficiency (PEI)

The faecal elastase or faecal fat test was used as a measure of the exocrine pancreatic function [19, 20]. PEI was defined as a fat excretion (aliphatic carboxylate [C14 C26]) > 25 mmol per 24 h or faecal elastase 1 level < 200 mg/g. Another alternative, ^{13}C labeled mixed triglyceride breath test was used and a percentage of $^{13}CO_2$ cumulative dose at 7 h below 5% confirms PEI [11]. Two studies demonstrated PEI as a significant and independent risk factor for sarcopenia [11, 19]. Olesen et al. demon strated that sarcopenia has a statistically significant asso ciation with opioid treatment ($p = 0.045$) and PEI ($p = 0.03$) on multivariate analysis [19]. An association between sarcopenia and PEI ($p < 0.001$)was displayed by Shintakuya et al. [11]. It should be noted that the results from this study, included all pancreatic diseases (malig nancy, neuroendocrine, and CP) [11].

Prevalence

The prevalence of sarcopenia from all studies ranged from 17 62% [11, 17 21].

Outcomes

The outcomes of sarcopenia in patients with CP are shown in Table 3. The quality of life (QOL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ C30) [23]. Bieliuniene et al. demonstrated that CP patients had notably more extensive pancreatic fibrosis (PF) ($p < 0.001$) and sarcopenia decreased QOL in CP patients [20]. Olesen et al. also showed that sarcopenia was asso ciated with reduced QOL, increased hospitalisation ($p = 0.07$), and reduced survival ($p = 0.005$) [19]. Sar copenia was associated with significantly lower islet yield and more peri operative blood loss ($p = 0.002$) following total pancreatectomy with islet autotransplantation in CP ($p = 0.001$) [21].

Table 1 Characteristics of studies examining the prevalence and impact of sarcopenia in chronic pancreatitis

Study	Title	Year	Study type	Location	CP population	Mean age	Newcastle–Ottawa Score#
Olesen et al. [19]	Sarcopenia associates with increased hospitalisation rates and reduced survival in patients with chronic pancreatitis	2019	Prospective, single institution	Aalborg, Denmark	182	57.4 ± 12.9 years	9
Shintakuya et al. [11]	Sarcopenia is closely associated with pancreatic exocrine insufficiency in patients with pancreatic disease	2016	Prospective, single institution	Hiroshima, Japan	132 (9 with CP) = 6.8%	73 years (median)	7
Bieliuniene et al. [20]*	CT- and MRI-Based Assessment of Body Composition and Pancreatic Fibrosis Reveals High Incidence of Clinically Significant Metabolic Changes That Affect the *Quality of Life and Treatment Outcomes* of Patients with Chronic Pancreatitis and Pancreatic Cancer	2019	Prospective, single institution	Lithuania	63 (CP) 37 (PDAC)	58 years	6
Trikudanathan, et al. [21] (conference abstract)	Pre-Operative Sarcopenia Predicts Low Islet Cell Yield Following Total Pancreatectomy with Islet Autotransplantation (TPIAT) for Chronic Pancreatitis	2019	Prospective, single institution	Minneapolis, United States	138	38 years	N/A
O'Connor et al. [18] (conference abstract)	Investigating the prevalence of sarcopenia in chronic pancreatitis in an Irish cohort: A CT-scan based pilot study	2014	Retrospective, single institution	Dublin, Ireland	29	43 years (median)	N/A
Bulanova et al. [17] (conference abstract)	CT assessment of sarcopenia in patients with pancreatic cancer and chronic pancreatitis	2012	Retrospective, single institution	Moscow	29 (CP) 20 (PDAC)	29–63 years	N/A

*The study population size was 100, which included both CP and PDAC patients

PDAC Pancreatic ductal adenocarcinoma

#NEWCASTLE—OTTAWA QUALITY ASSESSMENT SCALE

Discussion

This is a first review to examine the prevalence and impact of sarcopenia in patients with CP. In this review, sarcopenia has a prevalence of 17 64% in patients with CP. It has shown to have a statistical negative impact on various outcomes such as a lower QOL in CP patients with more than 50% pancreatic fibrosis, hospitalisation burden, mortality, and a lower islet cell yield following TPIAT.

Our findings indicate a paucity of research focusing specifically on sarcopenia and CP. We also found that there was major heterogeneity in the outcomes reported; however, the authors thought that all of the outcomes were important and had achieved statistical significance within respective studies. The included studies clearly support the hypothesis that sarcopenia negatively influence the outcomes of patients with CP. There is however limited evidence to provide a meaningful analysis in this review.

Sarcopenia is diagnosed when there is confirmation of low muscle quantity or quality; and is considered severe in addition of low muscle strength, and poor physical fitness [1]. The process of muscle tissue loss commences approximately at 40 years of age and progresses at a rate of 8% loss of muscle tissue per decade until the age of 70, which then accelerates to 15% thereafter per decade [24]. The pathophysiology of sarcopenia is complex and is attributable to reduction in caloric consumption, denervation of muscle fibres, intracellular oxidative stress, hormonal decrease, and enhanced myostatin signalling [9]. This review has demonstrated that sarcopenia is prevalent

Table 2 Results of studies on the measurement, prevalence, BMI, and muscle mass index of sarcopenia in patients with chronic pancreatitis

Study	Measurement of sarcopenia	Number or patients with sarcopenia (prevalence) *N* (%)	Mean BMI (SD), kg/m2	Sarcopenia (BMI < 18)	Sarcopenia (BMI > 25)	Median L3 muscle mass index (cm2/m2)
Olesen et al. [19]	Anthropometrics Bioelectric impedance, Hand grip, Up and go test	31 (17.0%)	20.9 ± 4.1	8	–	–
Shintakuya et al. [11]	CT axial images at L3 vertebral	37 (15%)	–	–	–	43.51 (male) 36.26 (female)
Bieliuniene et al. [20]	CT axial images at L3 vertebral	21 out of 63 patients (33.3%)	24.08 ± 4.5	6 / 21 (29%)	3 /21 (14%)	49.60 ± 7.5 (men)47.00 ± 8.6 (women)
Trikudanathan et al. [21]	CT axial images at L3 vertebral	46 out of 138 patients (33.3%)	–	–	–	–
O'Connor et al. [18]	CT axial images at L3 vertebral	15 out of 29 patients (52%)	25.6	6	7	–
Bulanova et al. [17]	CT axial images at L3 vertebral	18 (62%)	22.16 ± 2.3	3/18	2/18	–

in patients with CP and may be present in underweight, normal weight and obese patients. It is important to diag nose sarcopenia regardless of the BMI, as the presence of sarcopenia did not correlate with BMI values. Individuals of similar BMI display different percentages of lean and adipose tissue [25, 26]. Sarcopenic obesity is defined as a reduction in lean body mass in the context of excess fat [27], and it is easily overlooked in obese patients. Indi viduals who are obese and sarcopenic have worse outcomes than those who are sarcopenic and non obese [28]. Olesen et al. reported that 23(74%) of sarcopenic patients had a normal or obese BMI and demonstrated a significant association between sarcopenia and BMI subgroups ($p = 0.009$) [19].

The specificity and precision of body composition measurement modalities offer a new perspective to view the body habitus. Each has its own pros and cons in assessing changes in muscle or adipose tissue distribution. They provide a robust assessment for sarcopenia which is simple, feasible, and help facilitate development of com prehensive approaches to decision making regarding peri operative care [29]. Conventional anthropometric parame ters have a low index in detecting sarcopenia; however, it is not an accurate assessment of muscle tissue [30].

Conventional nutritional assessments also do not accu rately detect sarcopenia, and radiology has been proven to be more reliable [31]. The utilisation of radiology in the examination of body composition is highly differentiated, with the technology to recognise and discriminate between muscle, fat, as well as the distribution of adiposity within intermuscular, subcutaneous, and visceral sites [25]. Dual energy X ray absorptiometry (DXA) is feasible, accurate, non invasive, inexpensive, and regarded as the ideal standard for quantifying muscle mass [32]. However, the gold standards for non invasive measurement of muscle mass are magnetic resonance imaging (MRI) and CT [33]. The evaluation of sarcopenic obesity using CT data was introduced in 2013 [34], and is an objective and precise assessment of sarcopenia. The cut off points for the diag nosis of sarcopenia are arbitrary at this time; however, Prado et al. defined sarcopenia cut offs at approximately 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women [25]. The use of imaging to evaluate sarcopenia however does not assess the aspect of functional muscle status.

An alternative of measurement of body muscle/fat composition is a hand held bioelectric impedance analysis (BIA) machine that is affordable, widely available, and portable. It procures an evaluation of muscle mass based on whole body electrical conductivity [1]. In non obese adults, an accurate two compartment (lean, fat) measure ment of body composition can be made in 10 min with a BIA machine [35]. The studies in this review used CT imaging to detect sarcopenia and only one study used anthropometric measures. It should be noted, however, that sarcopenia is a relatively subjective measurement.

It is worth mentioning the impact of sarcopenia in pancreatic ductal adenocarcinoma (PDAC). Bieliuniene et al. included patients with PDAC and reported that a substantial number of cases of sarcopenia were detected in patients with CP (62%), demonstrating that sarcopenia was more prevalent in chronic diseases in contrast to malig nancy [20]. Shintakuya et al. took into account all pan creatic diseases (malignancy, neuroendocrine, and CP) [11]. Although they were analyzed separately in subgroups, this is a potential confounding variable. Recent meta analyses have shown sarcopenia (HR 1.49; 95%CI

Table 3 Results on the impact of sarcopenia in chronic pancreatitis

Study	Impact of Sarcopenia in CP	Hospitalisation	Mortality	Quality of life (QoL)
Olesen et al. [19]	PEI was an independent risk factor for sarcopenia ($p = 0.03$). Sarcopenia was significantly associated with opioid treatment ($p = 0.045$) and PEI ($p = 0.03$) on multivariate analysis	Increased risk of hospitalisation ($p = 0.07$), increased number of in-hospital days ($p < 0.001$). Sarcopenia was not associated with an increased *risk of pancreatitis related* hospitalisation during the follow-up period ($p = 0.39$)	Reduced survival ($p = 0.005$)	Decreased median (IQR) global health scores ($p = 0.003$)
Shintakuya et al. [11]	Sarcopenia was associated with PEI in men ($P < 0.001$) and women ($P = 0.012$) on univariate analyses. Only sarcopenia remained independently associated with PEI ($P < 0.001$) on multivariate analysis.**takes into accounts all pancreatic diseases (malignancy, neuroendocrine, and CP)	N/A	N/A	N/A
Bieliuniene et al. [20]	There was no significant difference in sarcopenia status among patients with CP and PDAC ($p = 0.85$). The presence of osteopenia/osteoporosis predicts the presence of sarcopenia ($p = 0.02$). Patients with CP had more pronounced pancreatic fibrosis (PF) ($p < 0.001$).** takes into accounts pancreatic malignancy	N/A	N/A	Lower QOL in patients with PF $\geq$ 50% and in the CP group. ($p < 0.001$)
Trikudanathan et al. [21]	Peri-operative blood loss was more common in sarcopenic patients as compared to non-sarcopenic patients ($p = 0.002$). Sarcopenia was associated with significantly lower islet yield following TPIAT ($p = 0.001$).	N/A	N/A	N/A
O'Connor et al. [18]	This preliminary study has shown a high prevalence of sarcopenia in CP, independent of BMI	N/A	N/A	N/A
Bulanova et al. [17]	Sarcopenia is highly prevalent in patients with pancreatic cancer and CP (66%) and may be present in patients with any BMI values	N/A	N/A	N/A

1.27 1.74, $p < 0.001$) and sarcopenic obesity (HR 2.01; 95%CI 1.55 2.61, $p < 0.001$) are significantly associated with worse overall survival in patients with PDAC [36]. A study has shown that sarcopenia is a strong predictor of the occurrence of pancreatic fistula and survival after pancre atoduodenectomy and recommends reconditioning of the sarcopenia prior to the operation [37].

Patients with CP potentially have a more pronounced level of malnutrition. Various factors such as intractable pain, alcoholism, malabsorption, and maldigestion from PEI, renders these patients at a consid erable risk for sarcopenia. Patients with CP are likely to have more co morbidities which may contribute to the loss of muscle mass and more adverse outcomes. CP was not properly defined except for one study which used the M Anheim assessment [19]. Nutritional assessment and the complications of CP are pivotal in the management of these patients. Approximately 30% 50% of CP patients have increment of resting energy expenditure [38]. The key strategy in these patients is the early detection of sar copenia and active interventions. The management involves a multidisciplinary team and includes alcohol abstinence, pain management, nutritional and dietary improvement, and pancreatic enzyme supplementation [39].

At this point in time, there is no evidence to suggest that sarcopenia can be treated or is modifiable. There is insuf ficient evidence available to guide the treatment of sar copenia. In a complex disease like CP, an optimal body habitus is unlikely to be achievable in the short term.

Nevertheless, the prognostic value of sarcopenia can be a valuable adjunct. Persons with sarcopenic obesity were evaluated with various exercise interventions (aerobic, resistance, and combined), and it was discovered that those in the resistance group showed the most improvements in strength [40]. The very first randomised controlled trial (RCT) is currently under study by the Japanese which evaluates the clinical influence of exercise therapy on sarcopenia in CP patients [41]. We await the results with anticipation.

Despite the relevant findings, this review has a few limitations. First, due to the paucity of data, conference abstracts were included to provide a more robust data for the review. The studies analysed were retrospective and prospective cohorts, and consisted of heterogeneous patient populations hence selection bias may be a limita tion. All studies were single centred, and consisted of a small patient population hence within each study, analysis remains a potential limitation. The large range of preva lence of sarcopenia reported across the studies may be due to how it was measured (large vs small population) and the duration the patients had been diagnosed with CP before they entered into the study.

Nevertheless, this review provides a platform to expand on this important prognostic factor. An increased effort is required to address the deficiency of research on this topic as evident in Table 3. Future studies should be designed to analyse the relevance of sarcopenia on the prognosis and management of CP patients by investigating the negative clinical outcomes. In addition, there is also a need for serial assessments of patients prospectively while attempting to treat their sarcopenia.

Conclusion

The review of these existing studies amalgamates the paucity of data on sarcopenia and its impact on CP. It has shown that sarcopenia is exceedingly prevalent and an important risk factor in CP patients. The data presented emphasises that sarcopenia has a significant prognostic value and should be included in future prospective analy ses on the outcomes of CP. There is a crucial need for more studies to address the deficiency of research on this topic and further elucidate the impact of sarcopenia in patients with CP.

Compliance with ethical standards

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

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Chapter 6

Conclusion

Chapter 6: Conclusion

This thesis aimed to investigate benign liver and pancreatic pathologies and to address the growing problem of these conditions on patients and the health care costs. This thesis provides the foundation for further work to be undertaken on these surgically challenging diseases.

The first publication revealed that ILLs are frequently encountered and contributes to the health care cost, and how to approach these in a sensible fashion with appropriate pathways. The current landscape for a good quality of care in these patients involves a thorough history taking; appropriate investigations to aid in the diagnosis, and timely surveillance scan. There is a need for a classification system, which stratifies ILLs by malignant potential based on a standardized and evidence-based approach.(49) A focus on resource allocation fosters for a better outcome for the patients and healthcare.

The third chapter discusses a novel entity – ITPN. Although it is a rarity, ITPN is premalignant and has demonstrated progression to invasive carcinoma.(10) The infrequent encounter of this variant poses a diagnosis challenge.(50) The scarcity of cases has yielded limited long-term data on survival, and therefore, the management strategies at present include a greater awareness of this diagnosis, surgical resection and close clinical surveillance to detect early recurrence. Further studies are essential to elucidate the natural history of ITPN to guide the best treatment strategy and determine survival.

This thesis also highlights gaps in current literature regarding the effects of VAT and sarcopenia in pancreatitis. Extensive literature exploring these outcomes has informed practice to improve the detection of these conditions, improve treatment outcomes and overall survival

in this cohort of patients. Investigating the alterations in body composition, physical function, and muscle strength in this population is a crucial step towards creating guidelines that is able to improve outcomes in the lives of these patients.

The systematic review established that VAT has an important prognostic indicator on the severity of AP.(42) However, it has not shown to be an independent risk factor to the risk of developing AP. The impact of VAT on the course and outcome of AP needs to be profoundly explored to confirm these findings, which may fuel earlier management and better define the prognosis of patients with AP. VAT may need to be incorporated into prognostic scores of AP to improve accuracy.

The fifth chapter presents the first systematic review ever conducted on sarcopenia and its impact on CP. It has shown that sarcopenia is exceedingly prevalent and an important risk factor in CP patients. The data presented emphasises that sarcopenia has a significant prognostic value and should be included in future prospective analyses in the outcomes of CP.(30) The main goals for treatment in this population are to maintain quality of life, prolong life, and reduce treatment-associated symptoms.

The significance of VAT and sarcopenia will continue to have an impact on various diseases. With this in mind, it is important that health professionals are aware of these factors and foster a holistic approach to patient care.

Ultimately, the provision of high-quality care depends on the inherent knowledge of these benign pathologies. Improvement in the quality of care involves a dedication by clinicians that

is integrated into learning and contributing to the current knowledge. Only then, more evidence-based practice guidelines and effective strategies can be implemented to improve outcomes of these patient populations. Until then, a multidisciplinary approach in an experienced hepatobiliary and pancreatic centre is recommended for the management of these complex benign conditions. Future studies and long term outcomes are paramount to improve patient outcomes and the sustainability of the healthcare system.

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