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Clinical Implications of the Celiac Artery Variations: MDCT Angiography Study on TRNC Population

Yasemin Küçükçiloğlu[1], Akinola Abraham Olonade[2], Mehtap Tiryakioğlu[2]

[1]Department of Radiology, Near East University Faculty of Medicine, Nicosia, North Cyprus

[2]Department of Anatomy, Near East University Faculty of Medicine, Nicosia, North Cyprus

Abstract

BACKGROUND/AIM: Variations in the origin, course, and branching pattern of the celiac trunk (CT) have been well-documented in various populations with clinical implications for surgical and radiological procedures in the abdomen. However, the prevalence and characteristics of CT variations in the Turkish Republic of Northern Cyprus population have not been well studied.

MATERIALS AND METHODS: Abdominal multi-detector computed tomography (MDCT) angiography examinations of 500 patients and were retrospectively evaluated by a radiologist in the radiology department of our hospital. The examinations were performed with a 256-detector CT scanner. A thorough evaluation of 108 patients was performed. Eighty-three of these patients were male (M), and twenty-five were female (F). The age ranges were from 19-78 (F: 26-78, M: 19-78).

RESULTS: Results showed that branching of the CT into the left gastric artery (LGA), common hepatic artery, and splenic artery is the predominant branching pattern in 74 patients 68.5%. However, variations in the branching pattern of the CT were observed in 34 patients 31.5% (30 M and 4 F). Furthermore, this study reported an unreported branching pattern of the CT, where a patient had the LGA originating from the right inferior phrenic artery; and this was associated with the gastrosplenic trunk.

CONCLUSION: Understanding the scope of these variations is of clinical importance in patients undergoing preoperative radiological evaluations, hepatic transplants, and open gastrostomies. Lack of awareness regarding these variations can significantly impact radiologic interventions and pre/post-operative planning of surgical procedures involving the gastrointestinal system.

Keywords: Celiac trunk, celiacomesenteric trunk, gastrosplenic trunk, hepatomesenteric trunk, anatomic variations, MDCT

INTRODUCTION

The celiac trunk (CT), which is the first anterior and often the largest visceral branch of the abdominal aorta (AA), arises immediately after the descending thoracic aorta passes through the aortic hiatus between the crura of the diaphragm at the level of the 12th thoracic vertebra posterior to the median arcuate ligament.[1,2] As noted by Marco-Clement et al.[3], an excellent understanding of the vascular anatomy of the abdominal cavity is crucial for surgical intervention on abdominal organs such as the liver, pancreas, spleen, etc. To underscore the importance of having a detailed awareness of vascular anatomy, Omar et al.[2] submitted that the presence of variations in the vascular supply of an organ impacts the surgical approach to intervention. Variations in the origin, course, branching pattern, and diameter of the CT have been well-documented in various populations with clinical implications for surgical and radiological procedures in the abdomen.[2] However, the prevalence and characteristics of CT variations in the Turkish Republic of Northern Cyprus (TRNC) population have not been well-studied.

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ORCID IDs of the authors: Y.K. 0000-0002-1572-1375; A.A.O 0000-0002-2345-3630; M.T. 0000-0001-7176-2764.

Corresponding author: Yasemin Küçükçiloğlu
E-mail: yasemin.kucukciloglu@neu.edu.tr
ORCID ID: orcid.org/0000-0002-1572-1375

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During embryonic development, CT forms due to the union of three arterial roots: the dorsal aorta, the vitelline artery, and the dorsal pancreatic artery. The embryological development of the CT begins in the fourth week of gestation when the primitive gut tube develops by folding and fusion of the endoderm and mesoderm layers. The dorsal aorta arises from the posterior aspect of the primitive heart and extends caudally, giving off segmental branches to the somites and intermediate mesoderm.[4] The vitelline artery, on the other hand, arises from the yolk sac and enters the embryo through the umbilical ring parallel to the gut tube. The dorsal pancreatic artery arises from the dorsal aorta and grows toward the developing pancreas. The fusion of these three arteries gives rise to the CT, which typically branches into the left gastric artery (LGA), the splenic artery (SA), and the common hepatic artery (CHA).[5] The complex and dynamic process of angiogenesis, vasculogenesis, and remodeling in the early embryo can lead to various CT variations, which have significant clinical implications for surgical and radiological procedures in the abdomen, such as trans-arterial chemoembolization (TACE) of the hepatopancreatic area, organ transplantation, metastatic tumor management.[6,7]

To date, no published study has investigated the prevalence and types of CT variations in the TRNC population, which has a unique geographical location and ethnic diversity. These variations can have significant clinical implications, affecting surgical and radiological procedures, and can lead to various iatrogenic pathologies if not properly understood. Detailed knowledge of the vascular anatomy of the CT is crucial to the success of many liver-related procedures. This knowledge provides a guide to the topography of liver vasculature, including procedural interventions such as TACE, trans-arterial radioembolization (TARE), and tumor resection. It is therefore imperative to examine the CT variations in the TRNC population using multi-detector computed tomography (MDCT) angiography and to compare the findings with the literature.

MATERIALS AND METHODS

Abdominal MDCT angiographies of 500 Turkish Cypriot patients were retrospectively evaluated, in the radiology department by a radiologist of our hospital. The examinations were performed with a 256-detector CT scanner (Somatom Definition Siemens Healthcare, Erlangen, Germany) with 120 mL of iodinated contrast material (Iobitridol, 350/200 mL, Guebert, Villepinte, France); scanning from the level of the diaphragm to the iliac bifurcation, using a bolus tracking system at the level of the descending aorta. The scanning parameters were as follows: kVp: 140, mAs: 34, slice thickness: 1 mm.

After excluding examinations of nonlocal patients living in TRNC and cases with an abdominal mass or who have undergone any surgical procedure, a thorough evaluation of 108 patients was performed. Eighty-three of these patients were male (M). Twenty-five were female (F), and the age ranges were between 19-78 (F: 26-78, M: 19-78).

The study was approved by the Near East University Faculty of Medicine Institutional Review Board (approval number: 2019/73-906, date: 24.10.2019). All participants included in this study provided informed consent.

Statistical Analysis

To analyze the variations of the CT, observed in this study, the classification approach of Ethiraj et al.[5] was followed. Five main branching patterns grouped into five types were identified in all 108 cases reviewed. Variations of the CT and its branches were noticed in 34 (31.5%) patients (30 M, 4 F). In addition, sub-branching patterns were further classified according to the main branching pattern with which they occurred. Using the Statistical Package for the Social Sciences software, descriptive statistics were used to calculate the frequencies and percentages of the branching patterns. The result obtained from the statistical analysis was tabulated and presented in Table 1.

Table 1. Five types of the CT's main branching pattern as well as the branching pattern of the subbranches, reported in this study

Type	Sub-type	CT's main branching pattern	CT sub-branching pattern/variation	n	%
1	a	Trifurcation	No variations	74	68.5%
	b	Trifurcation	rRHA from SMA	10	9.3%
	c	Trifurcation	LHA from LGA	6	5.6%
	d	Trifurcation	rLHA from LGA, accRHA from GDA	1	0.9%
	e	Trifurcation	Long CT, rLHAfrom LGA, accRHA from SMA	1	0.9%
	f	Trifurcation	accLGA from LHA	1	0.9%
	g	Trifurcation	Lat branch of LHA originated from LGA	3	2.8%
2		CMT		1	0.9%
3	a	GST + rCHA from aorta		4	3.7%
	b	GST	rLHA from LGA, GDA separately from the aorta, rRHA from SMA	1	0.9%
	c	GST	rRHA from SMA, rLHA, and rGDA originate from SA with a common trunk (rGDA separates at the level of porta hepatis)	1	0.9%
	d	GST + HMT		3	2.8%
4		HGT + SMT		1	0.9%
5		HST + GPT		1	0.9%
Total				108	100

CT: Celiac trunk, CMT: Celiacomesenteric trunk, GST: Gastrosplenic trunk, HMT: Hepatomesenteric trunk, SMT: Splenomesenteric trunk, HST: Hepatosplenic trunk, GPT: Gastrophrenic trunk, SMA: Superior mesenteric artery, LHA: Left hepatic artery, rCHA: Replaced common hepatic artery, rLHA: Replaced left hepatic artery, rRHA: Replaced right hepatic artery, LGA: Left gastric artery, accLGA: Accessory left gastric artery, rGDA: Replaced gastroduodenal artery, SA: Splenic artery, accRHA: Accessory right hepatic artery.

RESULTS

In Type 1a, we observed classical branching of the CT into the LGA, CHA, and SA, with no further observable variation in the distribution of the end arteries in 74 (68.5%) patients (Figure 1A). In Type 1b, a normal CT showing the origin of a replaced right hepatic artery (rRHA) from the superior mesenteric artery (SMA) was observed in 10 (9.3%) patients (Figure 1B). Type 1c showed a normal CT of a replaced left hepatic artery (rLHA) from LGA in 6 (5.6%) cases. Type 1d showed normal CT with rLHA originating from LGA and accessory right hepatic artery (accRHA) from the gastroduodenal artery (GDA) in 1 (0.9%) case (Figure 1C). Type 1e showed a normal CT with rLHA originating from LGA, an accRHA from SMA, present in 1 case (0.9%). Type 1f showing a normal CT with accessory left gastric artery (accLGA) from LHA was observed in 1 (0.9%) patient (Figure 1D), while Type 1g describes an abnormally long classical CT with the lateral branch of LHA originating from LGA in 3 (2.8%) patients.

In Type 2, we observed that the CT and SMA originated as a single trunk to form the celiacomesenteric trunk (CMT) in one (0.9%) patient (Figure 2).

Type 3a shows a gastrosplenic trunk (GST) + replaced CHA originating directly from the aorta in 4 (3.7%) patients. Also seen in a patient with this type of branching, was a long distance between the aortic orifice of the AA and CT of 7.7 cm (Figure 3A). Type 3b shows GST + rLHA originating from the LGA, GDA originating separately from the aorta, and rRHA originating from the SMA in 0.9% of cases. In Type 3c, we observed a GST with rRHA originating from SMA, while rLHA and replaced gastroduodenal artery (rGDA), originating from SA, were with a common trunk in 1 (0.9%) case (Figure 3B). It was also observed that the rGDA separates itself from adjacent structures at the level of the porta hepatis. Type 3d shows GST with hepatomesenteric trunks in 3 (2.8%) cases (Figure 3C). Type 4 shows hepatogastric trunk (HGT) alongside splenomesenteric trunk in one (0.9%) patient (Figure 4). Type 5 describes a hepatosplenic trunk (HST) with a gastrophrenic trunk [GPT-LGA, and right inferior phrenic artery (RIPA)] seen in 1 (0.9%) case (Figure 5).

DISCUSSION

One of the most consequential factors that impacts the outcome of surgical procedures is the proper understanding of the vascular anatomy of the area surgical intervention. A lack of detailed knowledge of vascular variations could result in negative patient outcomes or iatrogenic

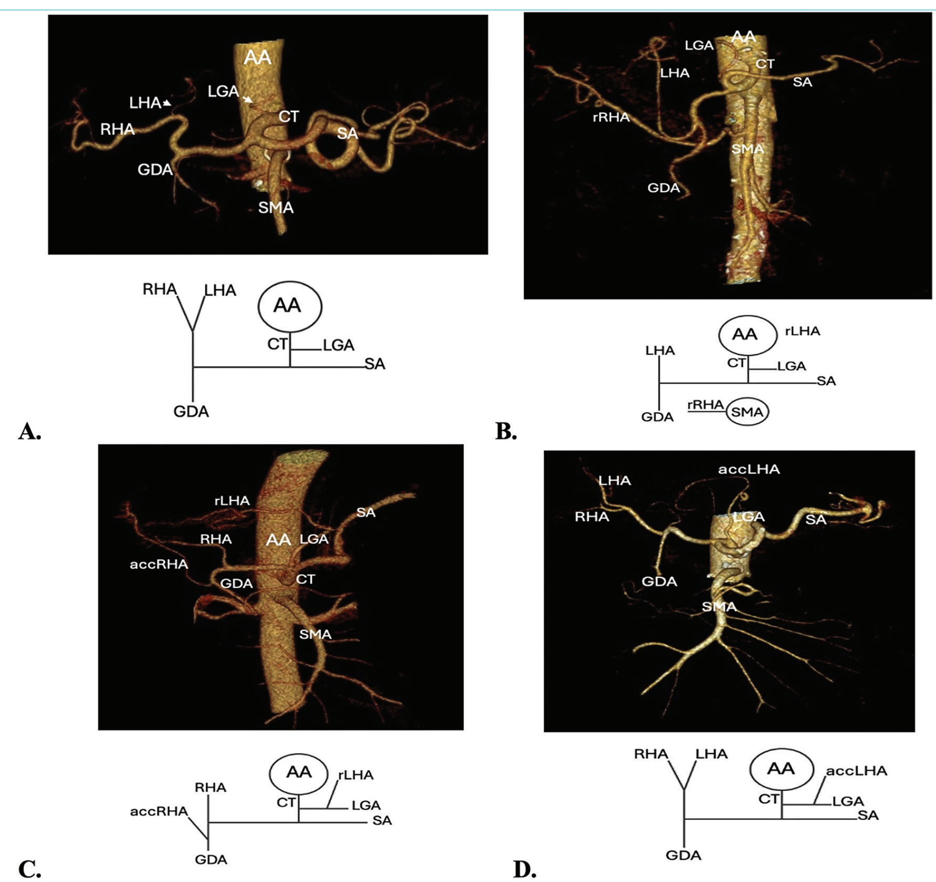

Figure 1. A. Type 1a shows abdominal aorta (AA), celiac trunk (CT), splenic artery (SA), left gastric artery (LGA), superior mesenteric artery (SMA), left hepatic artery (LHA), right hepatic artery (RHA), and gastroduodenal artery (GDA). **B.** Type 1b shows AA, CT, SA, LGA, SMA, LHA, replaced right hepatic artery (rRHA), and GDA. C. Type 1d shows AA, CT, SA, LGA, SMA, RHA, replaced left hepatic artery (rLHA), accessory right hepatic artery (accRHA), and GDA. D. Type 1f shows AA, CT, SA, LGA, accLGA, LHA, RHA, and GDA.

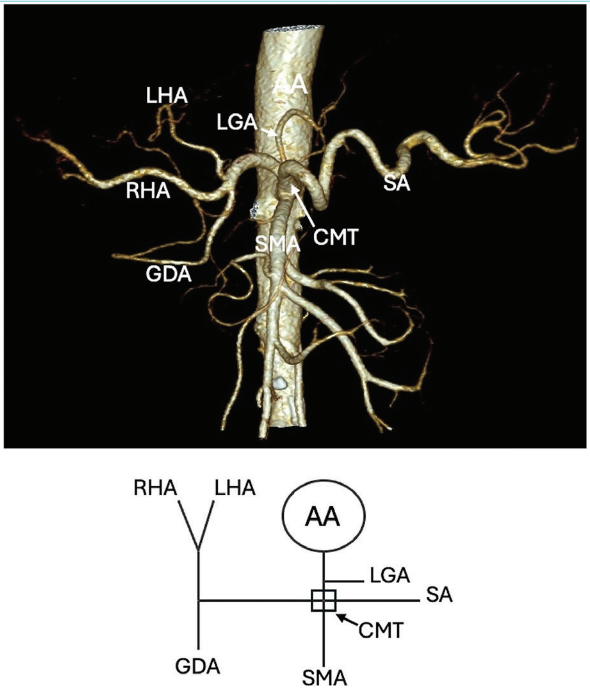

Figure 2. Type 2 shows abdominal aorta (AA), celiacomesenteric trunk (CMT), splenic artery (SA), left gastric artery (LGA), superior mesenteric artery (SMA), left hepatic artery (LHA), right hepatic artery (RHA), and gastroduodenal artery (GDA).

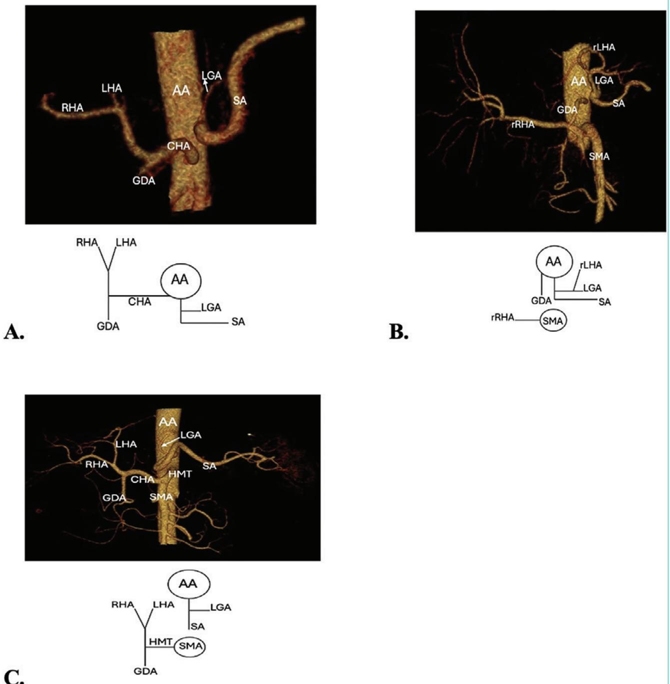

Figure 3. A. Type 3a shows abdominal aorta (AA), common hepatic artery (CHA), splenic artery (SA), left gastric artery (LGA), left hepatic artery (LHA), right hepatic artery (RHA), and gastroduodenal artery (GDA). **B.** Type 3c shows AA, SA, LGA, superior mesenteric artery (SMA), replaced left hepatic artery (rLHA), replaced right hepatic artery (rRHA), and replaced gastroduodenal artery (rGDA). C. Type 3d shows gastrosplenic trunk (GST) and hepatomesenteric trunk (HMT) originated from the AA.

injury to tissues and organs during surgical intervention.[8] According to Marco-Clement et al.[3], the clinical implications of having a thorough knowledge of the variations in the CT scans when planning for upper abdominal surgeries and radiological interventions are crucial to ensure a positive post-operative outcome in patients. Detailed awareness of the source, branching, and deviation from the norm of the CT is of utmost clinical importance when planning for surgical interventions such as digital subtraction angiography, as well as procedural interventions in the abdomen such as TACE, TARE, and tumor resection.[9] Omar et al.[2] acknowledged that precise knowledge of anatomical variations could determine surgical techniques and subsequent outcomes in patients. The study highlighted that lack of awareness regarding vascular variations can negatively impact surgical outcomes in patients. According to a case report by Roma et al.[10] published to elucidate the vascular anomalies of CT and its implications in the treatment of hepatocellular carcinoma using TACE, the importance of having detailed knowledge regarding the incidence, clinical and developmental significance of CT variations, particularly during invasive arterial procedures or abdominal surgeries, was highlighted. The study emphasized that precise identification of CT variations is germane for the success of surgical procedures such as endovascular treatment of unresectable malignant liver tumors and orthotopic liver transplantations. Ethiraj et al.[5] reported that an accurate understanding of the vascular anatomy and branching patterns of the CT in procedures involving splenectomy and gastrectomy using the Appleby technique can prevent iatrogenic injury of the CHA and mitigate the risk to surrounding vessels such as the mesenteric arteries.

The CT is a well-studied vessel due to its clinical and physiological importance in providing arterial blood to the foregut and its derivatives. As established in the literature, 15 variants of the CT have been identified.[8] Of all the variations of the CT, the trifurcation of the CT into CHA, LGA, and SA is considered the normal branching pattern.[5,9] Song et al.[11], in their study on CHA and CT variations in 5002 patients, observed 13 types of CT variations and reported the incidence of normal branching at 89.1%. Ugurel et al.[6] noted that the frequency of normal CT varies between 72% and 90%. In this study, as shown in Figure 1A, we observed that the normal branching of the CT in 74 patients (68.5%) was consistent with reports from numerous studies, which indicate that trifurcation of the CT into its classical branches remains the dominant branching type.[2,3] However, some studies have reported a lower incidence of this branching type.[5] Normal branching of the CT ensures adequate vascularization of abdominal organs, improves pre-operative and post-operative management techniques, and mitigates the risks of iatrogenic injuries that may occur during surgical manipulations in the abdomen.

Bifurcation of the CT has been observed and reported in the literature. According to Santos et al.[9], the incidence of bifurcation of the CT is 12%. However, in a retrospective study conducted on 100 patients by Ugurel et al.[6], 89% and 8% of the cases studied had trifurcation and bifurcation of the CT, respectively.[6] Their study also observed that accessory renal arteries increase the likelihood of variations in the CT and hepatic arteries.[6] Prakash et al.[12] reported the bifurcation of the CT into CHA and SA. Bifurcation of the CT can present enormous challenges to interventional radiologists and surgeons during preoperative procedural planning of transcatheter arterial chemoembolization in hepatic

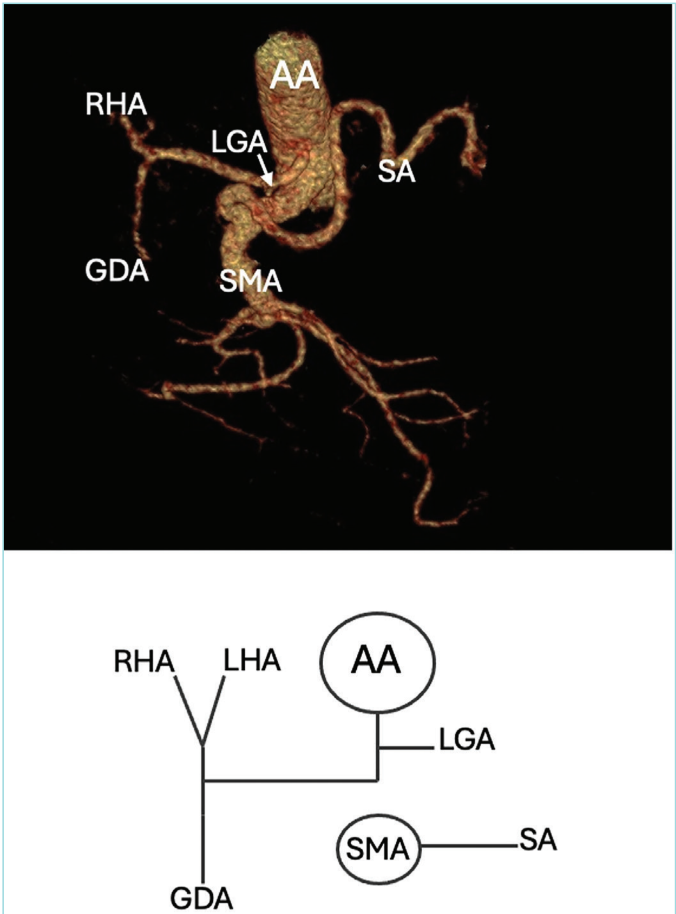

Figure 4. Type 4 shows abdominal aorta (AA), splenic artery (SA), left gastric artery (LGA), superior mesenteric artery (SMA), right hepatic artery (RHA), and gastroduodenal artery (GDA).

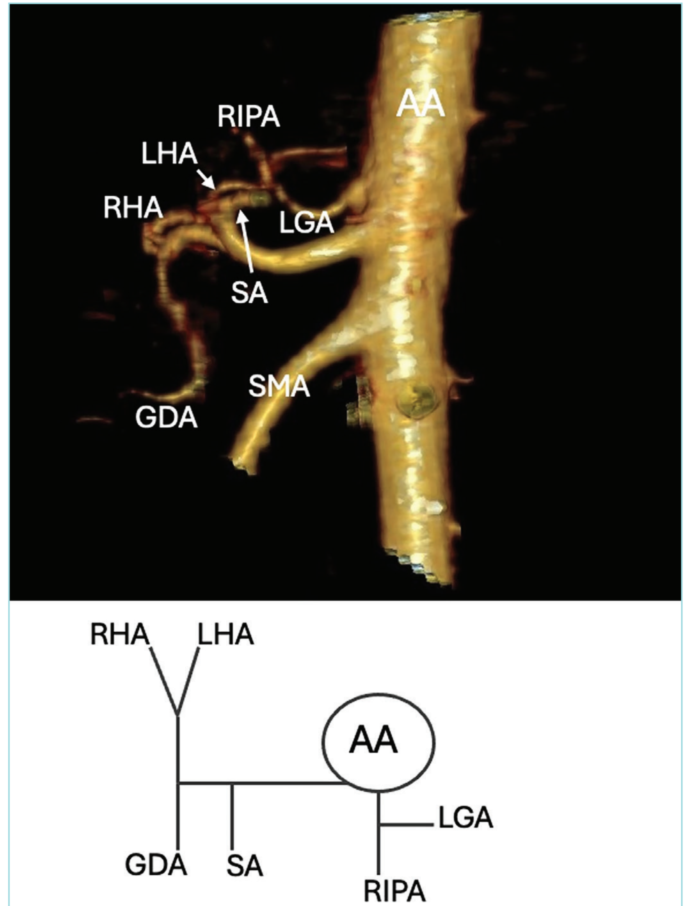

Figure 5. Type 5 showing abdominal aorta (AA), gastrophrenic trunk (GPT), hepatosplenic trunk (HST), splenic artery (SA), left gastric artery (LGA), superior mesenteric artery (SMA), left hepatic artery (LHA), right hepatic artery (RHA), replaced right inferior phrenic artery (rRIPA) and gastroduodenal artery (GDA).

tumors and liver transplants.[10] Iatrogenic injuries to abdominal viscera such as the liver, pancreas, spleen, and others due to postoperative complications of a bifurcated CT, have been reported.[6] According to a study by Pinal-Garcia et al.[13], the CT bifurcated in 7.1% of the cadaveric dissections. Bifurcation of the CT into the CHA and SA (HST), with the LGA originating from the AA, was seen in 33.3% of the cases observed. Bifurcation of the CT into SA and LGA (splenogastric trunk) was found in 25%, with the CHA arising from the SMA. Also, the study reported that the CT bifurcated into the CHA and LGA (HGT) while the SA arose from the SMA in 8.3% of the observed cases.[13]

In our study, we observed the bifurcation of the CT, which was named and classified according to the branches arising from the bifurcation point (Table 1). We observed the bifurcation of the CT into the HST with the LGA arising from RIPA as a GPT in 0.9% of the cases (Figure 5). To our knowledge, this branching variant has not been reported in the literature. In comparison, bifurcation of the CT into the GST was observed in 3.7% of the cases, with the CHA arising from the AA (Figure 3A). In a patient (0.9%), with the incidence of a GST, as shown in Figure 3B, we observed that the rRHA originated from the SMA, with an rLHA and rGDA originating from the SA. Complex sub-branching patterns, such as this, increase the challenges faced by surgeons and interventional radiologists during surgical procedures such as hepatobiliary carcinoma resection, liver resections, and hepato-pancreatico-duodenal interventional surgeries. Also, bifurcation of the CT, into the HGT with the SA arising from the SMA was observed in 1 patient (0.9%) (Figure 4).

The absence of an artery can impact the development and functioning of an organ if there is a lack of or insufficient collateral supply to that organ.[14] According to Marco-Clement et al.[3], the absence of CT does not have an embryologic explanation. It can present major clinical complications in patients with hepatocellular carcinomas, among other pathologies involving the abdominal region. This is especially concerning when there is poor collateral supply to compensate for the missing vessel, as the arterial supply to major organs is significantly altered.[2,9,15] Başar et al.[16] reported agenesis of the CT in which all the major organs that receive arterial blood from the CT and its branches were vascularized by a single artery. According to Van den Broecke et al.[17], CT is considered absent if the CHA, LGA, and SA arise independently from the AA. This study did not observe the complete absence of the CT in any of the patients evaluated. While rare, as noted by Omar et al.[2], the lack of CT can result in significantly altered blood supply to the stomach, pancreas, liver, spleen, and parts of the duodenum vascularized by its terminal branches. This type of variation can lead to the disruptive physiological functioning of these organs, complicating surgical interventions, and can result in fatal complications due to malnutrition and avascular necrosis of the affected organs.

The HST, described as the union of the CHA with the SA to form a common trunk with a separate LGA origin, was reported by Song et al.[11] as the most common variation of the CT. However, Ugurel et al.[6] found that the GST was the most observable variation (4%), followed by the HST (3%).

The GST as a variation of the CT is well reported: for example, Lipshutz[18] reported a GST with CHA arising from AA at an incidence of 4%, while Adachi reported a 2% incidence of a GST with CHA arising from the SMA.[19] Also, Song et al.[11] reported the incidence of GST as 0.22%. However, in our study, three patients had SMA originating from CHA (hepatomesenteric trunk) with GSTs, comprising 2.8% (Figure 3C).

There are reports of variants formed by the union of the CT with other branches of AA, in the literature. For instance, Adachi, in his study on 252 cadaveric specimens, reported a CMT, the union of CT and the SMA to form a single trunk, with an incidence of 2.4%.[19] Sangster et al.[14] reported that the presence of this type of variation deprives a patient of the dual vascular supply to the abdominal viscera: the liver, gall bladder, stomach, and parts of the small intestine, thereby elevating the risk of atherosclerosis or other vascular complications to the abdominal viscera. Marco-Clement et al.[3] attributed the development of this branching pattern to the persistence of large primitive ventral anastomoses between the developing superior mesenteric groups and the CT despite the regression of the 10th and 12th vitelline arteries. The scholarly report of Omar et al.[2] attests to this claim. Furthermore, a study by Matusz et al.[20] reported an unusual case in a small percentage of individuals where the CT originated from SMA. As shown in Figure 2, we observed the CMT in 1 patient (0.9%). Awareness of this variation among clinicians and interventional radiologists is of utmost importance during preparations for surgical interventions in the abdominal region, as it can significantly affect the blood supply to critical digestive organs.

Various classifications of CT variations, including types and subtypes, have been proposed, with some widely accepted among scholars and clinicians.[3,18] However, with the introduction of improved imaging techniques, the emergence and detailed observation of new variants that do not conform to established descriptions in the literature are on the rise. A study by Ugurel et al.[6] attributed the existence of such variants to complex embryogenesis involved in the development of the branches of the AA. In this study, the CHA originated directly from the aorta, while the LGA and SA branched off from the AA as the GST in four cases (3.7%) (Figure 3A). This variant supports the report of a study conducted by Lipshutz.[18] Ugurel et al.[6] highlighted the shared origin of branches of the AA to form a trunk. This variation is clinically significant due to the altered patterns of blood supply to the liver and intestines, which may influence procedural strategies for treating diseases in these organs.

Observations and reports of anomalous or accessory branches arising from the main branches of the CT have been documented. Our study observed and documented several variations in the branching pattern of the hepatic artery proper, one of the terminal branches of the CHA. In one patient, a rRHA arose as a branch of the SMA (Figure 1B), and an rLHA originated from the LGA. As shown in Figure 1C, a rLHA arose from LGA, while an accRHA branched from the SMA in a patient (0.9%). We also observed an abnormally long CT with an AA-CT distance of 7.7 cm. The incidence of this branching type can present a complex challenge to surgeons and interventional radiologists who lack awareness of it. In this case, the risk of iatrogenic injury to the CT is significantly elevated. In three patients, the anterior branch of the LHA originated from the LGA. Accessory LGA, is a rare variation of the LGA that should be kept in mind during the surgical interventions in the region particular to the aneurysms. It may originate either from the LGA or LHA.[21] In one case (Figure 1D), we observed the accLGA originating from the LHA (0.9%).

In some patients (10%), the rRHA originated from the SMA, while in others, 7% of the rLHA originated from the LGA. The percentage of appearance of rLHA was reported between 10-12% in Walker's[22] scholarly work, and Joshi et al.[23], and Kavitha[24] reported a 5% presence of rLHA in their studies. Ethiraj et al.[5] explained that branching of the right lateral hepatic artery (rLHA) from the LGA to supply segments 2 and 3 in left lobe donors is advantageous as it reduces the risk of injury to the remaining liver. However, Asif et al.[25] found that a rRHA can significantly increase the risk of thrombosis and hepatic artery stenosis in liver transplant recipients. This can increase the likelihood of iatrogenic injuries during surgical procedures like hepatobiliary hilar surgery, cholecystectomy, and pancreaticoduodenectomy.

Understanding the existence and extent of aberrant or accessory arteries in the body. A recent report by Cirocchi et al.[26] found that some patients undergoing preoperative radiological evaluations, hepatic transplants, and open gastrostomies had accessory or aberrant left hepatic arteries that originated from the left gastric arteries.

Failure to recognize these variations can have a significant impact on radiologic interventions and surgical procedures involving the gastrointestinal system, both before and after the operation.

Study Limitations

Our study has some limitations. The most important limitation is the small size of the study group. We believe that further studies with larger study groups may reveal previously unreported variations of CTA. The second limitation is the low quality of some figures, which can be attributed to patient or technical issues.

CONCLUSION

MDCT angiography enabled accurate and detailed observation of the vascular anatomy with CT. This study elucidated the variability of the celiac artery in the TRNC population and established the presence of previous unreported variations of clinical importance. CT variations can pose challenges for radiologists when interpreting imaging studies. Misinterpreting these variations may lead to inaccurate diagnoses of diseases and impaired treatment planning, underscoring the necessity of radiologists' familiarity with these anatomical anomalies. In the literature, a case exists where a rare CT variation played a crucial role in identifying an unknown deceased person. Therefore, understanding these variations can aid forensic experts in reconstructing the individual's identity and determining the cause of death.

Furthermore, surgical procedures involving the organs supplied by the CT are particularly affected by variations. Therefore, extensive knowledge of these variations of the CT is crucial in procedures such as liver transplantation and other surgical interventions, as it allows for better surgical planning and decreased postoperative complications.

MAIN POINTS

- The use of multi-detector computed tomography angiography enabled accurate and detailed observation of the vascular anatomy of the celiac trunk.

- This study elucidated the variability of the celiac artery in the Turkish Republic of Northern Cyprus population and established the presence of previously unreported variations of clinical importance.
- Misinterpreting these variations may lead to inaccurate diagnoses of diseases and impaired treatment planning, underscoring the necessity of radiologists' familiarity with these anatomical anomalies.

ETHICS

Ethics Committee Approval: The study was approved by the Near East University Faculty of Medicine Institutional Review Board (approval number: 2019/73-906, date: 24.10.2019).

Informed Consent: Patients signed informed consent regarding publishing their data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.K., Concept: Y.K., A.A.O., M.T., Design: Y.K., A.A.O., M.T., Data Collection and/or Processing: Y.K., A.A.O., M.T., Analysis and/or Interpretation: Y.K., A.A.O., M.T., Literature Search: Y.K., A.A.O., M.T., Writing: Y.K., A.A.O., M.T.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study had received no financial support.

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