

BRIEF COMMUNICATION: CELIAC AND SUPERIOR MESENTERIC ARTERIAL CALCIFICATIONS ARE PREVALENT IN PATIENTS WITH SUPRATHERAPEUTIC INTERNATIONAL NORMALIZED RATIO

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Abstract

Background: Common cause of supratherapeutic international normalized ratio (INR) is poor dietary intake of vitamin K by patients on warfarin. There is a vicious cycle wherein poor vitamin K levels in vivo can cause or worsen atherosclerosis while visceral artery atherosclerosis itself may interfere with adequate vitamin K absorption due to malabsorptive gastrointestinal tract.

Objectives: To assess the institutional prevalence of radiologically evident atherosclerotic calcifications of abdominal aorta and its visceral branches among supratherapeutic INR patients at our university hospital.

Materials and Methods: For this retrospective study, electronic medical records (EMR) for all patients aged 18 years and above were reviewed if they were managed for supratherapeutic INR (INR > 5.0) at our university hospital during one-year period, 2013. Supratherapeutic INR patients' EMR were accessed to delineate the patients who had any abdominal radiography of abdominal aorta and its branches during the two-year span, July 2012 to June 2014, to analyze evidence of abdominal aortic system's atherosclerosis (calcifications).

Results: A total of 108 supratherapeutic INR patients' EMR were analyzed. Visceral artery (celiac-superior mesenteric) calcifications were present in 51% patients with supratherapeutic INR. Among the patients with visceral artery calcifications (n = 55), both arterial systems were often involved with celiac artery's origin (91%), mesenteric artery's origin (64%), superior mesenteric artery's main trunk and branches (42%) and celiac artery's main trunk and branches (20%) in the descending order of observable calcifications' prevalence.

Conclusion: Prevalence of visceral artery calcifications in patients with supratherapeutic INR expects increased awareness among physicians to explore visceral artery atherosclerosis as underlying cause for poor vitamin K intake and uptake without overlooking the concurrent need for appropriately up-adjusted vitamin K requirements to potentially prevent the incidence of new-onset atherosclerotic calcifications or the worsening of pre-existent ones.

Keywords: Celiac Artery Calcification; Mesenteric Artery Calcification; Supratherapeutic INR; Vitamin K; Warfarin.

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Introduction

Supratherapeutic international normalized ratio (INR) is one of the common concerns when patients' anticoagulation is being managed with warfarin, a vitamin K antagonist¹. Common cause of supratherapeutic INR is poor dietary intake of vitamin K by patients on warfarin and it is recommended to ensure non-fluctuating daily amounts of dietary vitamin K to avoid non-therapeutic (subtherapeutic or supratherapeutic) INR levels². There is evidence that poor vitamin K levels in vivo can cause or worsen atherosclerosis³⁻⁹ especially in major arteries like abdominal aorta. Additionally, visceral artery atherosclerosis itself may interfere with adequate vitamin K absorption due to malabsorptive gastrointestinal tract¹⁰⁻¹². Therefore, for further exploration into this vicious cycle of upper gastrointestinal tract pathophysiology interacting with vitamin K, this retrospective study was designed with primary objective to assess the institutional prevalence of radiologically evident atherosclerotic calcifications of abdominal aorta and its visceral branches among supratherapeutic INR patients at our university hospital.

Materials and Methods

After institutional review board approval for retrospective study with waived consent, electronic medical records (EMR) for all patients aged 18 years and above were reviewed if they were managed for supratherapeutic INR (INR > 5.0) at our university hospital during one-year period, 2013. Supratherapeutic INR events' list was tabulated after extracting data from institutional EMR business system application tools/services. Subsequently, these supratherapeutic INR patients' EMR were accessed to delineate the patients who had any abdominal radiography of abdominal aorta and its branches during the two-year span, July 2012 to June 2014, i.e., six-months on either side of the year, 2013. Thereafter, if abdominal radiography was readable per limitedly experienced eyes of non-radiologist authors, EMR of such supratherapeutic INR patients were analyzed for patients' age, gender and body mass index (BMI), highest INR value achieved, and evidence of abdominal aortic system's atherosclerosis (calcifications) along

with any other intra-abdominal vascular pathology. Any documented gastrointestinal symptoms around the time of supratherapeutic INR were also recorded: reported weight loss; abdominal pain inclusive of postprandial pain and postprandial fullness; poor oral intake inclusive of aversion to food, loss of appetite, odynophagia and critical/terminal illness; nausea, vomiting and diarrhea; and other symptoms like constipation, bleeding per rectum and jaundice.

Statistical Analysis

The primary outcome of our analyzed data was to quantify prevalence of atherosclerotic calcifications of abdominal aorta and its visceral branches in supratherapeutic INR patients. Analysis of variance (ANOVA) for continuous data and Fisher's exact test for categorical data allowed the comparison between patients with observable intra-abdominal arterial calcifications and patients with non-observable intra-abdominal arterial calcifications so as to decipher p -value < 0.05 (if any) for statistical significance.

Results

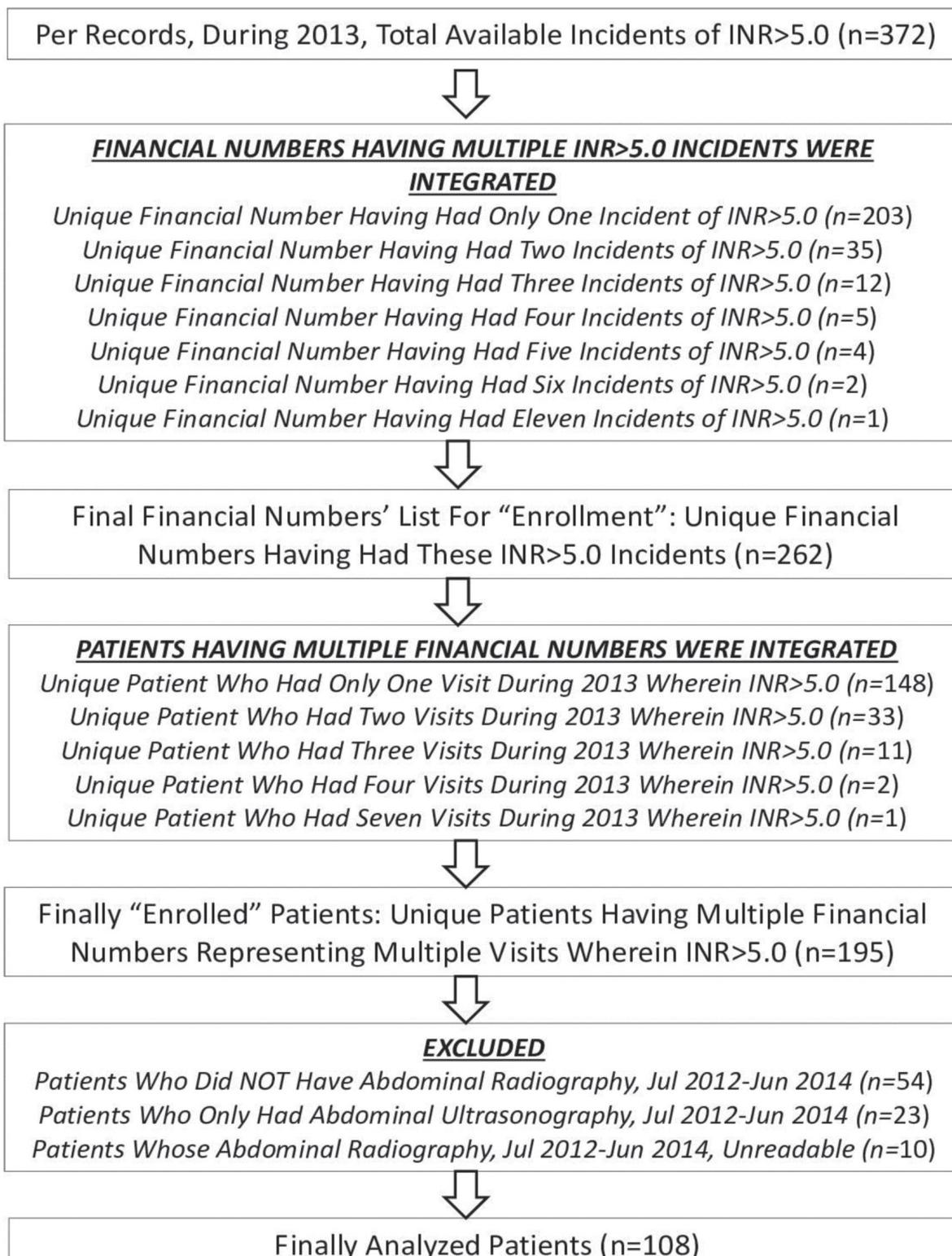
There were 372 recorded incidents of INR > 5.0 during the study period, 2013. Among these incidents, there were 262 unique financial numbers for hospital visits signifying that many financial numbers had multiple INR > 5.0 incidents. Subsequently, it was noted that overall there were only 195 unique patients having these 372 incidents of INR > 5.0 spread over 262 unique visits to our hospital. Essentially, during 2013, there were multiple patients who had multiple hospital visits during which they had multiple INR > 5.0 incidents (Figure 1).

During the corresponding two-year span, July 2012 to June 2014, 54 patients did not have any abdominal radiography while 23 patients only had abdominal ultrasonography and 10 patients' abdominal radiography was incomplete/unreadable per the limitedly experienced eyes of non-radiologist authors. Due to logistic reasons, experienced radiologists were not able to get involved in our study. Therefore, a total of 108 patients' EMR were finally analyzed for comparison wherein computed tomography (CT)

images of abdominal aorta and its visceral branches were clearly decipherable by the non-radiologist authors (Figure 1).

As detailed in Table 1, visceral artery (celiac-superior mesenteric) calcifications were present in 51% patients with supratherapeutic INR. Although the

Fig. 1
Patients' Flow Diagram



patients with visceral artery calcifications were older aged ($P < 0.001$), the more commonly evaluated upper abdominal images of CT-Thorax among younger patients ($P = 0.03$) might not have captured visceral artery calcifications distally. Among the patients with visceral artery calcifications ($n = 55$), both arterial systems were often involved with celiac artery's origin (91%), mesenteric artery's origin (64%), superior mesenteric artery's main trunk and branches (42%) and celiac artery's main trunk and branches (20%) in the descending order of observable calcifications' prevalence. Although 4% patients had coexistent abdominal artery dissection, the severity of visceral artery calcifications was not graded among the remaining patients because of limitedly experienced eyes of non-radiologist authors. The gastrointestinal

symptoms were commonly (constipation and jaundice) to very commonly (abdominal pain, poor oral intake, nausea, vomiting and diarrhea) present around the time of recorded highest INR but their prevalence were not significantly different whether patients' radiography demonstrated visceral artery calcifications or not.

Discussion

Our results indicate that supratherapeutic INR may serve as a prelude to investigate the presence of potentially under-diagnosed (though variably prevalent¹²⁻¹³) visceral artery pathologies. Supratherapeutic INR may also prompt providers to investigate whether vitamin K absorption being affected by visceral artery pathologies' related

Table 1
Patients characteristics. Data is presented as mean \pm SD or percentage (%)

Characteristic	Patients Without Obvious Abdominal Aorta Disease (n = 41)	Patients With Obvious Abdominal Aortic Disease Without Involving Celiac-Superior Mesenteric Arterial System (n = 12)	Patients With Obvious Abdominal Aortic Disease Involving Celiac-Superior Mesenteric Arterial System (n = 55)	P-Value
Age (in years)	49.9 \pm 12.1	61.1 \pm 11.5	67.1 \pm 11.9	< 0.001
Gender (F/M)	25/16	4/8	36/19	0.12
Body Mass Index (kg/m ²)	32 \pm 10.6	26.4 \pm 7.6	28.3 \pm 7.7	0.07
Multiple Admissions	22%	8%	22%	0.65
Highest INR Across Study Year (2013)	7.2 \pm 1.8	7.1 \pm 1.9	7 \pm 1.5	0.85
CT-Thorax's Upper Abdomen	34%	0%	20%	0.03
Gastrointestinal Symptoms Around The Time of Highest INR				
Reported New Weight Loss	5%	8%	0%	0.08
Abdominal Pain	15%	8%	11%	0.91
Poor Oral Intake	22%	25%	36%	0.32
Nausea	20%	0%	22%	0.22
Vomiting	17%	0%	13%	0.4
Diarrhea	10%	0%	13%	0.6
Constipation	5%	8%	9%	0.67
Bleeding per rectum	7%	0%	0%	0.13
Jaundice	2%	0%	4%	> 0.99

INR: International Normalized Ratio; CT: Computed Tomography.

gastrointestinal symptoms warrants supra-normal oral vitamin K requirements¹¹ in such patients. Moreover, the recurring incidents of supratherapeutic INR in spite of patients' and providers' presumptions about the adequacy of patients' oral vitamin K intake may be indirectly indicating (and "monitoring") the visceral artery pathologies' progression into malabsorptive states^{10,12}. Finally, when it becomes difficult to maintain INR within the therapeutic range, it may be worthwhile to explore alternatives to warfarin and other vitamin K antagonists so that vitamin K can be utilized to its fullest extent for its beneficial effects against vascular pathologies (and cardiovascular morbidity)¹⁴⁻¹⁵ without worrying for fluctuating INR (and anticoagulation efficacy) of calcification-promoting vitamin K antagonists¹⁶⁻¹⁷. It will be interesting to see in the future whether patients with visceral arterial pathologies, when sometimes not managed with vitamin K antagonists¹⁸⁻¹⁹, can be indirectly "monitored" by following-up on supra-normal (not supratherapeutic) INR levels which may implicate underlying deficient vitamin K intake in diet and/or its deficient uptake in gastrointestinal tract²⁰.

Our study has few limitations. It was a retrospective study wherein, to broaden the inclusion of supratherapeutic INR patients' CT images for research analysis, abdominal radiography was assessed over a larger window (two-year span) rather than limiting to the time around supratherapeutic INR that could have decreased the number of analyzed CT images. Therefore, it could not be clarified whether variable-onset and variably-progressing visceral artery calcifications were caused by or resulted in vitamin K deficiency. Future prospective research investigations by primary care physicians may have better opportunity to explore the visceral artery pathologies prior to initiating vitamin K antagonists and thereafter, with the help of hospitalists and critical care physicians, monitoring the incidence or progression of visceral artery pathologies when INR levels become supratherapeutic in these closely followed-up

patients. Educating primary care physicians along with hospitalists and critical care physicians in radiologists-supervised short training programs may help providers to screen and follow-up on patients' visceral arteries with the help of abdominal ultrasonography²¹ at bedside or in clinic. Our deficiencies as non-radiologists prevented our exploration into potential visceral artery pathologies among our patients who only had abdominal ultrasonography (n = 23). This could have been prevented if we had overcome our logistic limitations to involve specialist radiologists into our research. The involvement of specialist radiologists would have additionally helped the evaluation in visceral artery calcifications' graded quantification²²⁻²³ among our patients thereby accruing more appropriate clinical relevance to the visceral artery calcifications deciphered by our limitedly experienced eyes as non-radiologists. However, these limitations should not deter future prospective research collaborations among primary care physicians, hospitalists and critical care physicians trained in abdominal ultrasonography-based evaluation of abdominal aorta and its visceral branches for pathologies. Although CT imaging may be better at deciphering vascular pathologies²⁴, non-invasive and radiation-free ultrasonography-based screening and follow-up may be logistically better, more cost-effective and safer especially when repeated imaging may be warranted over time.

Conclusion

Prevalence of visceral artery calcifications in patients with supratherapeutic INR expects increased awareness among physicians to explore visceral artery atherosclerosis as underlying cause for poor vitamin K intake and uptake without overlooking the concurrent need for appropriately up-adjusted vitamin K requirements to potentially prevent the incidence of new-onset atherosclerotic calcifications or the worsening of pre-existent ones.

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