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Characterization of risk factors and timing of venous thromboembolism in patients with uterine carcinosarcoma

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Objectives: The purpose of this study was to evaluate the timing and risk factors associated with venous thromboembolism in women with uterine carcinosarcoma in a racially and ethnically diverse urban population. *Methods*: A retrospective cohort study was performed with all women diagnosed with carcinosarcoma from 2005–2018 at Montefiore Medical Center in Bronx, NY. Data regarding patient demographics, medical comorbidities, treatment course, Khorana score and timing of thromboembolic events were abstracted. A Cox proportional hazards model which included time-dependent covariates for treatment course variables was estimated to examine the association between patient-related variables and the incidence and timing of venous thromboembolism. *Results*: Forty (31%) of 130 included patients developed venous thromboembolism and there were no significant associations between patient demographics, medical comorbidities, or cancer treatment with thromboembolic events. Being within 6 weeks of surgery was associated with a higher hazard of venous thromboembolism (HR 3.8, 95% CI [1.09–13.50], $P = 0.04$). Thirty-two (80%) patients who developed venous thromboembolism did so outside of the perioperative window. Patients receiving chemotherapy with a Khorana score $\geq$2 had a significantly increased risk of developing venous thromboembolism (HR 3.5, 95% CI [1.30–9.23], $P = 0.01$). *Conclusions*: Patients with uterine carcinosarcoma have a high risk of thromboembolic events throughout the entire disease course and were found to be at greatest risk during the 6 weeks following surgery. Although no patient or treatment-related factors were associated with an increased risk of venous thromboembolism, we found that the Khorana score may be helpful in identifying patients who may benefit from thromboprophylaxis while receiving chemotherapy.

Keywords

Uterine carcinosarcoma; Venous thromboembolism; Khorana score; Thromboprophylaxis

1. Introduction

Uterine carcinosarcoma is a rare and aggressive tumor that accounts for approximately 15% of deaths from cancer of the uterine corpus despite representing only 4–5% of the burden of uterine malignancy [1]. The development of venous thromboembolism is a significant contributor to increased morbidity and mortality in gynecologic cancer patients with uterine carcinosarcoma [2, 3]. The risk of venous thromboembolism in women with gynecologic malignancies has been shown to be associated with aggressive disease characteristics including advanced stage and high-risk histology, as well as patient-related factors such as advanced age, obesity, Black race, and comorbid cardiovascular disease [4–6]. Moreover, the development of venous thromboembolism during a woman's disease course has been associated with worse survival outcomes [4–6]. Patients with uterine carcinosarcoma are at a high risk of venous thromboembolism as it commonly affects older women, is characterized by aggressive histological features, and presents at an advanced stage in 60% of cases [1]. Additionally, uterine carcinosarcoma is more prevalent amongst Black women and it has recently been shown that Black women are at the highest risk of developing cancer-associated venous thromboembolism [1, 7].

Although the incidence of venous thromboembolism in women with uterine carcinosarcoma has been previously reported as 8%, no studies have examined the timing of venous thromboembolism throughout the disease course or the efficacy of venous thromboembolism risk prediction tools such as the Khorana score [8, 9]. Because the risk of venous thromboembolism remains high for up to one year after initial surgical staging, previous studies have hypothesized that long-term prophylaxis may be beneficial in preventing venous thromboembolism in women with high-grade uterine tumors [10].

The primary objectives of our study were to characterize the risk factors associated with the development of venous thromboembolism and to describe the timing of thromboembolic events during the disease course in women with uterine carcinosarcoma. The secondary objective of this study was to evaluate the efficacy of the Khorana scoring system for predicting venous thromboembolism in this population.

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2. Materials and methods

Institutional review board approval was obtained from Albert Einstein College of Medicine (AECOM) to review all patients diagnosed with uterine carcinosarcoma at Montefiore Medical Center from 2005 to 2018 as identified from the AECOM Montefiore Medical Center Gynecologic Oncology tumor registry. All patients with histological confirmation of uterine carcinosarcoma via surgical pathology or biopsy report were included in the study. Patients were excluded from the study if their medical record was found to be incomplete or insufficient for data collection and analysis.

In order to characterize risk factors potentially associated with the development of venous thromboembolism in these women, several variables were abstracted from the medical record including patient demographics, medical comorbidities, and details of surgical, radiation, and chemotherapy treatments. Patient-related factors that were extracted included age, race, body mass index (BMI, calculated as weight (kg)/[height (m)]^2) at the time of presentation, and chart-indicated comorbidities that have previously been identified as known risk factors associated with venous thromboembolism (diabetes, hypertension, hyperlipidemia, cardiovascular disease, prior venous thromboembolism, smoking history, chronic obstructive pulmonary disease, and chronic kidney disease). The surgical data that were collected included cancer stage, type of surgery (minimally invasive versus open surgery), the radicality of surgery (category 1: hysterectomy and bilateral salpingo-oophorectomy only; category 2: additional node resection or tissue biopsy; category 3: additional omentectomy or appendectomy; category 4: additional tumor debulking), evidence of residual disease, and hospital discharge with pharmacologic anticoagulation prophylaxis. Adjuvant treatment data were collected including chemotherapy regimens and radiation type (external beam radiation only, brachytherapy only, or external beam radiation plus brachytherapy). All of these risk factors were analyzed for an association with a diagnosis of venous thromboembolism.

The timing of venous thromboembolism was evaluated by first identifying the patients who developed thromboembolic events and then examining when these events occurred in relation to cancer treatment. Thromboembolic events were identified and defined as radiographically confirmed cases of deep vein thrombosis or pulmonary embolism on venous duplex ultrasonogram, computed tomography (CT) scan, and/or ventilation-perfusion scan. Patients were censored if they did not develop evidence of venous thromboembolism by the date of last follow-up (date of last healthcare visit shown in the electronic medical record), date of death, or the end of the study period. Each thromboembolic event was categorically sorted into one of six groups to characterize when events occurred with respect to disease course: (a) venous thromboembolism diagnosed at presentation (within 1 week of cancer diagnosis), (b) venous thromboembolism diagnosed during neoadjuvant chemotherapy, (c) venous thromboembolism diagnosed during the 42-day postoperative period (the postoperative period is defined as 42 days because insurance at our institution establishes postoperative visits at 2 weeks and 6 weeks after surgery), (d) venous thromboembolism diagnosed during adjuvant chemotherapy, (e) venous thromboembolism diagnosed during adjuvant radiation therapy, and f) venous thromboembolism diagnosed after treatment. Thromboembolic events were characterized as occurring "during treatment" if they occurred between the first date of the treatment cycle and 3 weeks after the last date of the treatment cycle; events that occurred beyond three weeks of the last date of treatment were categorized as "after treatment".

For women who underwent chemotherapy, the Khorana score was retrospectively calculated in order to evaluate the efficacy of the Khorana scoring system for predicting venous thromboembolism [8]. The Khorana score is a predictive tool that stratifies patients receiving chemotherapy into low (score of 0), intermediate (score of 1 or 2), or high (score of 3 or greater) risk categories for developing thromboembolic events. The Khorana score was calculated using information regarding primary cancer type (1 point is given to patients with gynecologic malignancies) as well as the following items extracted from the medical record: a point was added to the composite score when the pre-chemotherapy BMI was greater than or equal to 35 kg/m^2, pre-chemotherapy platelet count was greater than or equal to 350 $\times$ 10^9/L, the pre-chemotherapy hemoglobin level was less than 10 g/dL, or the pre-chemotherapy leukocyte count was greater than 11 $\times$ 10^9/L.

Summary statistics were computed for all variables of interest. To examine the association between patient, tumor and treatment characteristics and incident venous thromboembolism, univariate cause-specific Cox proportional hazards models were estimated. Deaths prior to venous thromboembolic events or censoring were treated in the model as a competing risk, therefore patients were censored at the time of death. Time-dependent covariates for treatment course variables (peri-surgery, peri-chemotherapy, and peri-radiation periods) were utilized in the model via a counting process approach to examine the association between treatment and the incidence and timing of venous thromboembolism. In exploratory analyses, multivariable models were examined. A model consisting of *a priori* factors of interest as well as those factors that were statistically significant in the univariate analysis is presented. A cumulative incidence function (CIF) using the Fine Grey approach was generated to summarize the cumulative incidence of venous thromboembolism over the course of the study period [11]. All analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The LIFETEST procedure was used to estimate the cumulative incidence function and the PHREG procedure was used to model cause-specific hazards. Two-sided *P*-values less than 0.05 were considered statistically significant.

Table 1. Patient demographics for women diagnosed with uterine carcinosarcoma from 2005–2018 (n = 130).

Characteristic	Total cohort (n = 130)	No VTE (n = 90)	VTE (n = 40)
Age (y)	67.7 ± 8.6	67.2 ± 8.2	68.4 ± 9.3
BMI (kg/m^2)	31.1 ± 6.9	30.4 ± 5.9	32.8 ± 8.5
Total no. of medical comorbidities*	3 (2–4)	3 (2–4)	3 (2–3.3)
Medical comorbidities			
Diabetes	58 (45)	42 (47)	16 (40)
Hypertension	111 (85)	79 (88)	32 (80)
Hyperlipidemia	63 (48)	49 (54)	14 (35)
Cardiovascular disease	35 (27)	30 (33)	5 (13)
Prior VTE	9 (7)	5 (6)	4 (10)
Smoker in the past year	2 (2)	1 (1)	1 (3)
COPD	9 (7)	5 (6)	4 (10)
Chronic kidney disease	15 (12)	13 (14)	2 (5)
Obesity	75 (58)	50 (56)	25 (63)
Race			
White	21 (16)	15 (17)	6 (15)
Black	73 (56)	48 (53)	25 (63)
Hispanic	26 (20)	17 (19)	9 (23)
Other or unknown	10 (8)	10 (11)	0 (0)
Cancer stage			
I	46 (35)	35 (39)	11 (28)
II	9 (7)	4 (4)	5 (13)
III	39 (30)	24 (27)	15 (38)
IV	31 (24)	22 (24)	9 (23)
Unstaged	5 (4)	5 (6)	0 (0)
Surgical characteristics†			
Minimally invasive	32 (26)	22 (26)	10 (26)
Open surgery	92 (74)	64 (74)	28 (74)
Chemotherapy treatment††			
Received chemotherapy	100 (77)	67 (74)	33 (83)
Khorana score = 1	41 (41)	34 (50)	7 (22)
Khorana score = 2	38 (38)	23 (34)	15 (45)
Khorana score = 3+	21 (21)	10 (15)	11 (33)

VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; BMI, body mass index.
Data are mean ± SD, median (interquartile range), or n (%) unless otherwise specified.
*Composite score includes diabetes, hypertension, hyperlipidemia, cardiovascular disease, prior VTE, recent smoking history, chronic obstructive pulmonary disease, chronic kidney disease, and obesity.
†For the 124 participants who underwent surgery.
††Khorana scores were only analyzed in the 100 patients who received chemotherapy.

3. Results

One hundred thirty patients with uterine carcinosarcoma were identified for inclusion in the study (Table 1). The median age in the study population was 67 years (IQR 61–74) and the median BMI was 31 kg/m^2 (range 15–57). The majority of the cohort self-identified as Black race (56%), and only 21 (16%) identified as being of white race. For women who received chemotherapy (n = 100), the median Khorana score was 2 (range 1–5) at the initiation of treatment.

There were no significant associations between demographic variables such as age, BMI, or Black race with the development of venous thromboembolism (P = 0.39, 0.27 and 0.40, respectively). Additionally, there were no associations between the pre-existing medical comorbidities extracted and incidence of venous thromboembolism on the bivariate analysis (Table 2). The univariate analysis suggested that cardiovascular disease and having multiple comorbidities were protective against the development of venous thromboembolism (HR = 0.26 95% CI [0.09–0.74], P = 0.01; HR = 0.81 95% CI [0.66–0.99], P = 0.05, respectively). However, these associations did not retain significance in the multivariate analysis. Surgery type and stage of disease were not associated with a higher hazard of venous thromboembolism in this cohort (0.82 and 0.32, respectively).

A total of 40 patients (31%) developed radiologically confirmed venous thromboembolism during the study period. Twenty-seven (68%) of these patients were diagnosed with lower extremity deep venous thrombosis, 10 (25%) patients

Table 2. Cause-specific hazard ratios for incident venous thromboembolism in women with uterine carcinosarcoma (38 events; n = 128).

Characteristic	HR (95% CI)	*P*-value
Age	1.02 (0.981–1.06)	0.39
BMI	1.03 (0.98–1.08)	0.27
Total no. of medical comorbidities*	0.81 (0.66–0.99)	0.05
Diabetes	0.96 (0.50–1.82)	0.96
Cardiovascular disease	0.26 (0.09–0.74)	0.01
Prior VTE	1.07 (0.33–3.50)	0.91
Smoker in the past year	1.31 (0.18–9.60)	0.79
COPD	1.09 (0.33–3.60)	0.88
Chronic kidney disease	0.32 (0.08–1.33)	0.12
Obesity	1.02 (0.53–1.98)	0.95
Race		
White	Ref.	
Black	1.48 (0.60–3.60)	0.40
Other	0.98 (0.34–2.90)	0.98
Stage of disease		
I–II	Ref.	
III–IV	1.40 (0.72–2.71)	0.32
Surgical characteristics†		
Minimally invasive	Ref.	
Open surgery	1.09 (0.51–2.30)	0.82
Received chemotherapy††		
Khorana score = 1	Ref.	
Khorana score ≥ 2	3.46 (1.30–9.23)	0.01

VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; BMI, body mass index.

*Composite score includes diabetes, hypertension, hyperlipidemia, cardiovascular disease, prior VTE, recent smoking history, chronic obstructive pulmonary disease, chronic kidney disease, and obesity.

† For the 124 participants who underwent surgery.

††Khorana scores were only analyzed in the 100 patients who received chemotherapy.

Table 3. Time-dependent cause-specific hazard ratios for incident venous thromboembolism in women with uterine carcinosarcoma (38 events; n = 128)*.

Characteristic	HR (95% CI)	*P*-value
Surgery time period		
No surgery within 6 weeks	Ref.	
Perisurgical period	3.83 (1.09–13.50)	0.04
Chemotherapy time period		
No chemotherapy within 3 weeks	Ref.	
During chemotherapy	0.89 (0.36–2.20)	0.80
Radiation time period		
No radiation within 3 weeks	Ref.	
During radiation	1.95 (0.54–7.00)	0.31
Anticoagulation Prophylaxis†		
Did not receive prophylaxis	Ref.	
Received prophylaxis	1.24 (0.60–2.55)	0.57

* The two thrombotic events that occurred at presentation were excluded in this analysis.

†Received during the postoperative period.

were diagnosed with pulmonary embolism, and 3 (8%) patients were diagnosed with upper extremity deep venous thrombosis. Of these patients, 2 cases of venous thromboembolism (1 pulmonary embolism and 1 lower extremity deep venous thrombosis) were found incidentally on computed tomography scan for routine evaluation of tumor progression. Of those diagnosed with venous thromboembolism during the study period, 11 (27.5%) had stage 1 disease, 5 (12.5%) had stage 2 disease, 15 (37.5%) had stage 3 disease, and 9 (22.5%) had stage 4 disease. Thirty-three (33%) patients who received chemotherapy (n = 100) developed a venous thromboembolism. Twenty-six (78%) of these patients who developed venous thromboembolism while receiving chemotherapy had a Khorana score of $\geq$2.

Regarding the categorical timing of thromboembolic events, four (10%) cases of venous thromboembolism were diagnosed at presentation, 2 (5%) during neoadjuvant chemotherapy, 8 (20%) during the 42-day postoperative window, 6 (15%) during adjuvant chemotherapy, 2 (5%) during adjuvant radiation, and 18 (45%) after completion of adjuvant treatment. Seven (87.5%) of the 8 women who developed venous thromboembolism within the 42-day postoperative window had open surgery, and 1 (12.5%) had minimally invasive surgery. In total, 80% of women who developed venous thromboembolism did so outside of the perioperative window.

Because there was an insufficient sample to perform a detailed analysis of the association between postoperative anticoagulation and the development of venous thromboembolism, descriptive statistics were generated from our data. Of the 124 patients who underwent surgery, 37 (30%) were discharged home with venous thromboembolism prophylaxis. Eleven (30%) of these patients developed thromboembolic events during their disease course-1 (9%) patient developed venous thromboembolism during neoadjuvant chemotherapy, 3 (27%) patients during the 42-day postoperative window, 3 (27%) during adjuvant chemotherapy, 1 (9%) during adjuvant radiation, and 3 (27%) after completion of adjuvant treatment.

Being within 42 days of surgery was associated with a higher hazard of incident venous thromboembolism (HR = 3.83, 95% CI [1.09–13.50], P = 0.04) (Table 3). The enhanced venous thromboembolism risk during the perisurgical period retained statistical significance in all adjusted models, including those adjusting for the number of patient risk factors, cardiovascular disease, BMI, and history of venous thromboembolism (Table 4).

Undergoing radiation (or within 3 weeks of radiation ending) was associated with a higher hazard of incident venous thromboembolism; however, this was not statistically significant (HR = 1.95, 95% CI [0.54–7.00], P = 0.31). Receiving chemotherapy (or within 3 weeks of ending chemotherapy) was not associated with a higher hazard of venous thromboembolism (HR = 0.89, 95% CI [0.36–2.20], P = 0.80). How-

Table 4. Multivariable model for incident venous thromboembolism in women with uterine carcinosarcoma.

Characteristic	HR (95% CI)	*P*-value
Surgery time period		
No surgery within 6 weeks	Ref.	
Perisurgical period	4.05 (1.10–14.50)	0.03
BMI (*continuous*)	1.05 (0.99–1.10)	0.05
Total no. of medical comorbidities* (*continuous*)	0.81 (0.59–1.10)	0.18
Cardiovascular disease	0.38 (0.11–1.30)	0.13
Prior VTE	1.30 (0.38–5.20)	0.62

VTE, venous thromboembolism; BMI, body mass index.

* Composite score includes diabetes, hypertension, hyperlipidemia, cardiovascular disease, prior VTE, recent smoking history, chronic obstructive pulmonary disease, chronic kidney disease, and obesity.

Table 5. Estimated cumulative incidence of venous thromboembolism in women with uterine carcinosarcoma.

Time (months)	Cumulative incidence of VTE	95% CI
3	0.087	(0.046–0.145)
6	0.128	(0.076–0.193)
9	0.153	(0.096–0.222)
12	0.187	(0.124–0.262)
18	0.235	(0.162–0.315)
24	0.276	(0.197–0.361)

VTE, venous thromboembolism.

ever, patients receiving chemotherapy with a Khorana score $\geq$2 had 3.5 times the hazard of developing a venous thromboembolism compared to those receiving chemotherapy with a Khorana score of 1 (HR = 3.46, 95% CI [1.30–9.23], P = 0.01).

Examination of the overall cumulative incidence function for venous thromboembolism in Table 5 shows increasing incidence over a 24-month period with an estimated venous thromboembolism incidence of 0.128 (95% CI [0.076–0.193]) at 12 months post disease staging and 0.276 at 24 months (95% CI [0.197–0.361]). A visual representation of the overall cumulative incidence function for venous thromboembolism over a longer, 175 month period is shown in Fig. 1.

4. Discussion

Our study demonstrated that the risk of venous thromboembolism in women with uterine carcinosarcoma is very high during all time points along the continuum of disease, and was significantly associated with the 42-day period following surgery. As 80% of women who developed venous thromboembolism did so outside of the perioperative window, our study suggests that the risk of venous thromboembolism remains high throughout the entire disease course. Although chemotherapy treatment was not found to increase the risk of venous thromboembolism in our study population, those patients receiving chemotherapy with a Khorana score $\geq$2 were at an increased risk of developing venous thromboembolism compared to patients undergoing

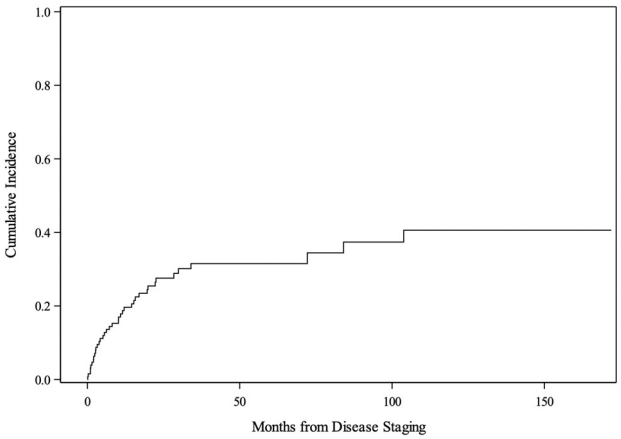

Fig. 1. Cumulative incidence of venous thromboembolism in women with uterine carcinosarcoma over a 175-month period accounting for the competing risk of death.

chemotherapy with a Khorana score <2. Our result suggests that the Khorana score may be valuable in identifying patients who could benefit from thromboprophylaxis while receiving chemotherapy. There was a small association between radiation treatment and venous thromboembolism; however, this was not statistically significant. Because this small association occurred in the context of a low event rate, radiation may be an important risk factor to consider in larger, prospective studies. There were no patient-related factors or tumor-related factors associated with an increased risk of venous thromboembolism.

The incidence of venous thromboembolism in our study was 31%. This result is substantially higher than the previously reported venous thromboembolism rate of 8% found in a multi-institutional study of 906 patients with uterine carcinosarcoma from 1993–2013 [9]. Of note, Matsuo *et al.* [9] found that obesity and non-Asian race were associated with higher risks of venous thromboembolism. The discrepancy in venous thromboembolism rate between studies may be explained by the vast differences in study demographics. Although these factors were not found to be statistically significant within our own study population, it is possible that the combination of our low event rate and demographic makeup of largely Black (56%) and Hispanic (20%) patients did not allow for a statistically powerful comparison against other races of interest. Approximately 53% of the cohort in the Matsuo *et al.* [9] study was of Asian race and was represented by the lowest by-race venous thromboembolism rate of 3.1%. Their study found that patients of Black race had the highest venous thromboembolism incidence at 21.4%, but this subpopulation represented only 9.3% of their cohort. The majority of our study population was composed of patients of Black race, included very few Asian patients and included a high burden of obesity. Therefore, this may explain why our rate of venous thromboembolism is higher than previously reported.

Our study also suggests that the risk of venous thromboembolism in women with uterine carcinosarcoma may be

greater than the risk of venous thromboembolism in other uterine tumor histologies. Venous thromboembolism has been evaluated at our institution for women with uterine serous carcinoma, which reported an incidence of venous thromboembolism of 17% [10]. It is possible that the specific histological features or disease patterns associated with carcinosarcoma may put women at a higher risk for venous thromboembolism. One proposed mechanism for venous thromboembolism development in women with uterine carcinosarcoma is the presence of epithelial-mesenchymal transition in distant sites throughout the body that may be controlled by the same inflammatory cytokines involved in venous thromboembolism formation [9].

Limitations of our study include those inherent to a retrospective study. Uterine carcinosarcoma is a rare tumor and therefore the total number of cases available for analysis was limited at our institution. Given the low event rate in our cohort of 130 patients, robust multivariable modeling was not able to be performed. Multivariable models were considered exploratory and were observed to be qualitatively consistent with the univariate results with respect to statistical significance. Regarding the retrospective study design, we were unable to confirm adherence with anticoagulant treatment medications and cannot make definitive claims regarding causality between risk factors and venous thromboembolism diagnosis.

Our study contributes significantly to the literature by describing the timing of thromboembolic events in women with uterine carcinosarcoma. Additional strengths include our ability to evaluate the impact of chemotherapy and radiation therapy on venous thromboembolism formation in our cohort. This analysis also illustrates the efficacy of the Khorana scoring system for predicting venous thromboembolism and represents a racially and ethnically diverse urban population that is often understudied.

5. Conclusions

Our study demonstrates that women with uterine carcinosarcoma are at high risk of developing venous thromboembolism throughout their disease course, with the greatest risk being within the 6 weeks following surgery. No patient-, tumor-, or treatment-related factors were found to be associated with a higher risk of thromboembolic events. The Khorana score may be useful in identifying patients at high risk for venous thromboembolism while undergoing chemotherapy treatment. Our study generates the hypothesis that women with active uterine carcinosarcoma may benefit from venous thromboembolism prophylaxis in the postoperative period and while receiving adjuvant treatment. Large prospective studies are needed to further test this hypothesis.

Author contributions

RB is the first author of the manuscript. She performed the data collection and was principally involved in the preparation of the manuscript. GMG, NV, KYL, DYK and MF served as co-authors on the manuscript and made substantial contributions and revisions to the final draft. NSN is the lead author on the manuscript and was involved in the supervision of the design, data collection, analysis and preparation of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Institutional review board approval was obtained from Albert Einstein College of Medicine (AECOM).

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Conflict of interest

The authors declare no conflicts of interest.

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