Patients with MEN1 are at an increased risk for venous thromboembolism

VTE risk in MEN1

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ABSTRACT

Background: Multiple endocrine neoplasia type 1 (MEN1) is a rare inherited disorder predisposing to the development of multiple functional and non-functional neuroendocrine tumors (NETs). Only uncommon MEN1-associated functional NETs such as glucagonomas (<1%) and ACTH-producing tumors (<5%) are known to be associated with hypercoagulability. It is unknown if patients with MEN1 generally have increased risk of VTE.

Methods: We queried a prospective natural history study of germline mutation positive MEN1 patients (n=286) between 1991-2019 for all lifetime events of VTE. Search terms were: DVT, thromb, embol, PE, pulmonary embolism, clot, hematology consult, anticoagulant, coumadin, lovenox, xarelto, warfarin, aspirin, rivaroxaban and apixaban. Incidence rates were calculated accounting for age and sex. Comparison was made to published incidence rates in healthy populations, different types of cancer, and Cushing's syndrome.

Results: Thirty-six subjects (median age 45 years, range 16-75) experienced a VTE event, yielding a prevalence rate of 12.9%. The age-sex adjusted incidence rate of VTE is 9.11 per 1,000 patient-years, with a sex-adjusted lifetime incidence rate of 2.81 per 1,000 patient-years. MEN1-associated lifetime incidence rates are ~two-fold higher than the estimated annual incidence rate in the general population and are comparable to known risk in the setting of various types of cancer. Approximately 80% were diagnosed with pancreatic NETs, of which 24% were insulinomas. Fourteen patients (42%) experienced peri-operative VTE events.

Conclusions: MEN1 patients have an increased risk of VTE. Further mechanistic investigation and validation from other MEN1 cohorts are needed to confirm the increased prevalence of VTE in MEN1.

Keywords: MEN1, venous thromboembolism, pancreatic neuroendocrine

INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is a multi-tumor syndrome which manifests as hyperfunctioning parathyroid glands (90%) as well as the development of neuroendocrine tumors (NETs) of the anterior pituitary (30-40%) and/or gastroenteropancreatic system (30-70%)[1]. It is most commonly caused by a germline pathogenic variant in the *MEN1* gene (11q13)[2]. A majority of the pancreatic NETs (pNETs) in the context of MEN1 are non-functional. However, functional tumors such as gastrinomas and insulinomas, or other, less common, glucagonomas, vasoactive intestinal peptide tumors (VIP-oma), and somatostatinomas, can result in clinically evident endocrine symptoms.

Hypercoagulable events can be life threatening and are estimated to account for between 60,000 to 100,000 deaths in the United States alone[3]. Various functional syndromes and carcinomas have been linked to an increased risk of venous thromboembolism (VTE). For example, hypercortisolism within the context of Cushing's syndrome (CS) has been associated with a significantly increased risk of VTE compared to the general population[4]. A high incidence of VTE is reported among metastatic pancreatic adenocarcinoma patients compared to patients with other cancers[5]. However, it is unknown if patients with germline *MEN1* mutations have an increased risk of developing VTE, which includes both deep-vein thrombosis (DVT) and pulmonary embolism (PE).

Rare pancreatic tumors occurring in MEN1 patients (<1%) include glucagonomas, which are known to have a higher risk for VTE (up to ~30%)[1,6]. In addition, only ~2-4% of MEN1 patients will have adenocorticotropic hormone (ACTH) excess (caused by either functional pituitary adenomas or bronchial/duodenalpancreatic NET), while <1% will have adrenal (ACTH-independent) CS[7,8]. Primary hyperparathyroidism, which is the most

prevalent manifestation in patients with MEN1, has rarely been reported to be associated with VTE[9] and is not clinically associated with thromboembolic events. Non-functional pNETs have been associated with local tumor thrombosis[10], but not with systemic VTE[11].

MEN1 patients are susceptible to other risk factors for VTE, including multiple major surgeries in a lifetime, frequent hospitalization, or the possibility of a concomitant active non-neuroendocrine malignancy[5,12,13]. In this study, we aimed to assess the incidence and prevalence of VTE in a cohort of germline mutation positive MEN1 patients at a single institution. Our database was queried for lifetime and study-time hypercoagulable events. Patient history, risk factors, and etiology for the development of VTE were evaluated to determine if our patient population experienced increased rates of clotting episodes as compared to the general population and others with known hypercoagulable conditions.

PATIENTS AND METHODS

Study Population

All subjects included in this analysis provided written informed consent to participate in a long-standing ongoing hyperparathyroidism natural history protocol (NCT00001277) that was initiated in 1991. Only patients with a known pathogenic germline mutation in the *MEN1* gene were included in the analysis. Patients were excluded from the analysis if data were unextractable from the electronic medical record system and/or the study investigators were not able to ascertain if an event had occurred. A select number of patients had participated in a previous NIH hyperparathyroidism protocol initiated in the 1970s but were subsequently signed onto the more recent version of the protocol, providing data from prior to 1991. Patients were typically evaluated every 1-2 years at the NIH for standard of care surveillance (including a history and physical, biochemical testing, and radiological imaging) until either the patient declines further assessment or death.

Data Collection

Definitions. A venous thromboembolism event was defined as a deep venous thrombosis and/or pulmonary embolism. Arterial thrombosis was not included in this analysis. Diagnosis was confirmed by either physician documentation and physician review (for events occurring prior to enrollment to the NIH protocol) or by study-team evaluation at NIH for events occurring during protocol follow-up. All lifetime VTE events were included in the analysis. A sub-analysis included events which occurred specifically during study-time follow up at our institution.

Hypertension was considered as per the American Heart Association guidelines[14]: blood pressure >130/80 or the prescription of anti-hypertensive medications. Diabetes was defined as per the American Diabetes Association guidelines[15]. Body mass index (BMI) was calculated from medical records at the time of VTE event or initial presentation to our institution if the event occurred prior to protocol enrollment. A well-characterized sub-cohort of *MEN1* germline mutation positive patients (n=83) who had not experienced VTE events was analyzed for possible MEN1-specific phenotype risk factors (incidence of NETs, surgery, etc.) as well as common VTE risk factors (diabetes, hypertension, BMI, age, and sex). This subset of the larger MEN1 cohort included patients who had recently (within the past 1-2 years) undergone an annual evaluation at our institution and whose life-long MEN1 manifestations, current biochemical data, and radiological imaging were chart-reviewed and recorded in a newly-implemented patient database.

Data extraction. In order to determine which patients had a VTE event, the electronic medical record system was queried using the following search terms: deep vein thrombosis and/or DVT, thromb, embol, pulmonary embolism and/or PE, clot, anticoagulant, coumadin, lovenox, xarelto, warfarin, aspirin, rivaroxaban, apixaban, and hematology consult.

Additional data collected in order to well-characterize both the VTE and non-VTE sub-cohort included: number of parathyroid surgeries, number of pituitary surgeries, incidence of pituitary hormone hypersecretion, number of abdominal surgeries, and incidence of gastroenteropancreatic tumors and hormone hypersecretion. Additionally, biochemical data from within ±12 months of initial VTE event were collected and included serum ionized calcium, parathyroid hormone, gastrin, prolactin (if prolactinoma), insulin (if insulinoma) and chromogranin A levels. When available, serum glucagon levels were recorded. All biochemical data and MEN1 manifestations for the non-VTE MEN1 sub-cohort were collected during patients' last presentation to our institute, within 1-2 years of present analysis.

Comparative analysis. We carried out a PubMed search to identify a large cancer cohort study for comparison. In addition, we pulled data on CS studies to ascertain the hazard among this high VTE-risk population. The lifetime risk was ascertained from all 36 subjects who experienced a VTE event, while the study-time risk was calculated based on the 26 subjects who had a VTE event while enrolled in the protocol.

Statistical analysis. Statistical analyses were performed using SPSS (version 21; Armonk, NY: IBM Corp.). Alpha was set at 0.05. Data are presented as mean with 95% confidence interval (CI) or frequency (percentage). The Kaplan-Meier 'time-to-event' method was used to calculate survival curves between VTE and non-VTE MEN1 cohorts. Incidence rates were calculated both on the basis of age and study follow-up time, and then expressed per 1,000 person-years. The Chi-squared test or the Fisher exact test were used to evaluate differences between VTE and non-VTE MEN1 cohorts for clinical manifestations as appropriate.

RESULTS

Risk factors among MEN1 patients with VTE

A total of 286 germline mutation positive MEN1 patients had available medical records for review. Two hundred and forty-two records had no mention of either PE or DVT in physician notes or radiology review. Eight patients were excluded due to records containing insufficient data to determine whether a VTE event had occurred or not. Thirty-six (12.9%) patients were identified to have experienced at least one lifetime VTE event. Of these, 11 (30.1%) patients had a DVT alone, 12 (33.3%) patients had a pulmonary embolism (PE), and 13 (36.1%) patients had both PE and DVT. The mean age at the first VTE event was 46.4 years old (age range 16 – 78 years) and there was no obvious gender preference (50% female) (**Table 1**).

Most events (44.4%) occurred in patients between the age of 30-50 **(Figure 1A**). However, three patients had VTE events prior to the age of 20: a 16-year-old female had undergone a distal pancreatectomy for insulinoma as well as a parathyroidectomy within nine months of developing a PE (died at age 21 due to suicide); an 18-year-old male developed a DVT and PE nine years prior to being diagnosed with MEN1 with unknown disease manifestations at that time (died at age 37 due to unknown causes); a 19 year old female experienced both DVT and PE six years prior to being diagnosed with MEN1 and Zollinger-Ellison syndrome. There were no differences in rates of general risk factors including hypertension, type 2 diabetes mellitus, overweight/obese BMI, and smoking history between the VTE cohort and the non-VTE MEN1 cohort (**Figure 1B**).

At the time of data collection, 7/36 (19.4%) patients with VTE had died: one death was confirmed to be due to large bilateral PEs, one was the aforementioned death by suicide, another was associated with metastatic pancreatic adenocarcinoma, and the remaining four

causes of death were undocumented. Kaplan-Meier analysis revealed no significant difference (p = 0.93) in survival between the VTE (mean survival=77.3 years, CI: 70.5-84.1) and non-VTE MEN1 cohort (mean survival=81.0 years, CI: 76.4-85.5), although protocol follow-up data was not systematically collected (**Figure 2**).

MEN1 peri-operative events. While half of all patients had undergone at least 1 abdominal surgery for an MEN1-related NET prior to or at the time of VTE, 15 (41.6%) of the documented VTE events were within 3 months of an in-patient operation and were thus considered peri-operative. Nine of the peri-operative VTE events were related to abdominal surgeries (1 hysterectomy, 3 subtotal/distal pancreatectomies, 3 Whipple procedures, and 2 duodenectomies). The remaining 6 peri-operative events included a thoracotomy, an esophageal operation, a total parathyroidectomy, a trans-sphenoidal surgery, a pelvic floor repair, and a hip replacement. Data on prophylactic anti-coagulation use was not available. There were no reported cases of neuroendocrine carcinoma.

A standard hematological work-up was performed in incidental or non-provoked VTEs (n=21). Two patients were identified to have factor V Leiden mutation (1691 G to A), 2 had abnormally low protein C activity (42% and 48%, reference 59-144%), 1 had abnormally low protein S activity (42% reference 55-134%), 3 tested positive for lupus anticoagulant, 2 had low antithrombin III activity (50 and 62%, reference 63-138%), 3 had high fibrinogen (553-738 mg/dL, reference 177-466 mg/dL), and 4 had high erythrocyte sedimentation rates (49-94 mm/hr, reference 0.0-25.0 mm/hr). In addition, 7 (19.4%) patients had reported one or more family members with MEN1 and VTE. Of those patients, only 1 inherited factor V Leiden mutation was identified.

MEN1-related manifestations among VTE and non-VTE cohorts

VTE cohort manifestations. Among the VTE cohort, twenty-one (58.3%) patients had a diagnosed pituitary adenoma: 9 prolactinomas, 1 thyroid stimulating hormone-secreting adenoma (TSH-oma), and 11 non-functioning lesions (**Table 1)**. There were 6 documented pituitary surgeries prior to or at the time of VTE. No patient had active ACTH-dependent or -independent CS at the time of VTE. All patients (100%) were diagnosed with primary hyperparathyroidism at the time of their initial event, with 30 (83.3%) patients having had at least 1 parathyroid surgery (range from 1 to 5) prior to or at the time of VTE. Twenty-nine (80.1%) patients had documented diagnoses of pNETs, of which 7 were diagnosed as insulinomas and the remaining were non-functional. None had glucagonoma. Sixteen patients (44.4%) had diagnosed gastrinoma and/or Zollinger-Ellison syndrome, and 7 (19.4%) were diagnosed with metastatic neuroendocrine disease.

Non-VTE cohort manifestations. Fifty-four (65%) patients had pituitary adenomas at the time of analysis, including 13 prolactinomas, 1 TSH-oma, 1 ACTH-secreting tumor, 1 growth hormone (GH)-secreting tumor, and 38 non-functioning lesions. Fourteen (16.9%) patients had pituitary surgery (range of 1 – 2). All but two patients (97.6%) had diagnosed hyperparathyroidism at the time of analysis, with 69 (83.1%) having had at least one parathyroid surgery (range of 1 – 5) within their lifetime. Seventy-nine (95.2%) had diagnosed pNETs, including 4 (5.1%) insulinomas while 36 (43.3%) had diagnosed gastrinoma and/or ZE. Twenty-eight (33.7%) had diagnosed metastatic neuroendocrine disease.

Comparative analysis among MEN1 patients. Evaluating manifestations among well-characterized patients with MEN1 (n=83) and those who experienced VTE found no significant differences between pituitary adenoma diagnosis, number of pituitary surgeries, hyperparathyroidism diagnosis, number of hyperparathyroid surgeries, metastatic neuroendocrine disease, or gastrinoma diagnosis and/or Zollinger-Ellison syndrome (**Figure 3**). The presence of pNETs was significantly different between cohorts, with the non-VTE cohort demonstrating more pNETs versus those who had a VTE (95% vs. 80%, respectively; p<0,05). In addition, patients who had a VTE had a higher incidence of insulinomas (25% vs. 5% in non-VTE; p<0.05).

Risk Evaluation: Cancer, Cushing's Syndrome, General Population and MEN1

The overall study-time risk was 9.11 per 1,000 person-years, adjusted for age and sex. The sex-adjusted incidence rate of a lifetime VTE event for a patient with MEN1 was 2.81 per 1,000 person-years. The lifetime risk is ~2-fold the estimated population incidence rates for VTE among healthy people (**Table 2**)[16,17]. We performed a comparative analysis from the literature focusing both on the lifetime and study-time risk of VTE in MEN1.

It is established that cancer and Cushing's Syndrome (CS) are both associated with an increased risk for the development of VTE[4,5,8,12,18,19]. The pooled incidence rate of VTE in various types of cancer are on average between 3.8 – 8.8. The adjusted study-time risk of VTE in MEN1 is similar to the incidence rates at the higher end of the spectrum (seen in hematological cancers such as leukemia) and are similar to the rates seen in CS within 1-30 years after diagnosis.

DISCUSSION

The present analysis demonstrates that germline mutation positive MEN1 patients in a single-center cohort study have a lifetime incidence rate two-fold than that of the general population and a study-time incidence rate that is comparable to known VTE risk occurring in cancer patients and long-term risk in CS. While MEN1 patients are likely at an increased peri-operative risk, no distinguishing gender, hematological profile or population risk factor clearly clustered to signal increased VTE risk. There were significantly less non-functional pNETs and more patients with insulinoma (although not gastrinoma) within the VTE cohort as compared to the non-VTE MEN1 cohort. In interpreting this data on the incidence of pNETs, it is important to note that the non-VTE cohort have been evaluated with highly sensitive somatostatin nuclear imaging (^{68}Ga-Dotatate PET/CT) within the past three years, while the VTE cohort was analyzed retrospectively and less than one half have had highly sensitive nuclear imaging which may detect more pNETs. Thus, the detection of pNETs could be explained by imaging differences. However, pNET functionality diagnoses (e.g. insulinoma and gastrinoma) have been stable over time, and likely represent true differences between cohorts.

The majority of patients who developed VTE had MEN1-related manifestations of disease that mirror known prevalences[1], including all patients presenting with a history of hyperparathyroidism, ~60-80% with pNETs, and ~50% with pituitary adenoma at the time of VTE event. The number of patients with insulinoma in the VTE cohort is 2-fold higher than the predicted incidence of ~10-15% of cohort studies that have been confirmed in large MEN1 center databases[1,20]. In long-term outcome data of MEN1 patients with insulinoma[20], thrombosis was not mentioned as a complication post-surgery.

MEN1 is considered a relatively indolent multi-neuroendocrine tumor syndrome. A paucity of data related to the risk of VTE in the setting of hereditary and non-hereditary

neuroendocrine tumors limits the ability to directly compare risk. Therefore, evaluating the range of incidence rates among a variety of cancer types, including colorectal, prostate, solid tumors, breast, and hematological, provides useful cross-comparisons[21].

Pancreatic carcinomas are known to have high VTE incidence rates and may provide pathophysiological clues[12,22]. Pancreatic adenocarcinoma, for example, is thought to contribute to a hypercoagulable state by inducing the inflammatory response and activating procoagulant factors such as platelet factor 4 (PF4), tissue factor (TF), and plasminogen activator inhibitor type 1 (PAI-1)[23]. Patients with increased TF expression experience VTE at a rate of 26.3% compared to that patients with low TF expression at 4.5%[23,24]. In fact, high levels of TF have been found by immunohistochemistry on pituitary adenomas[25] but have never been explored in other NETs. It remains unknown whether TF or other pro-angiogenic factors may contribute to either VTE or the increased rate of local thrombosis that is seen in pNETs[10,11].

An alternative hypothesis may include a role for c-MET, a hepatocyte growth factor receptor that is highly expressed on neuroendocrine tumor cells with a biallelic loss of *MEN1*[26]. Pre-clinical data in mice with liver-specific overexpression of an activated cytoplasmic form of c-MET demonstrated multiple clonal tumor expansions with a two-phase thrombo-hemorrhagic event: initially with identification of multiple venous thromboses which then evolved into hemorrhagic diatheses[27]. Further analysis by gene expression profiling indicated increased induction of *PAI-1* and cyclooxygenase-2 (*COX-2*) genes, both of which normally inhibit clot degradation, leading to a pro-thrombotic state. Further evidence for c-MET in NET as an inducer of *PAI-1* or *COX-2* are needed in order to delineate a mechanistic link between c-MET and VTE.

ACTH-dependent hypercortisolemia occurs in <5% of MEN1 patients[28] with a low peri-operative transsphenoidal surgery (TSS) risk[8]. Only 1 patient in our MEN1 cohort experienced a VTE following TSS for a macroprolactinoma. Meta-analysis has failed to demonstrate a link between the severity of hypercortisolemia and incidence of VTE[4]. Additionally, no one in our cohort had active CS during the study-time, indicating that CS most likely does not account for the increased risk of VTE in this investigation.

In the context of the general population, the incidence of post-operative VTE is dependent on the patient's condition prior to surgery, type of surgery, and patient age, with an increased incidence in patients who are over 65 years old[16]. In a retrospective analysis evaluating patients who underwent surgeries of various lengths under general anesthesia (n=1,432,855) the overall rate of post-operative VTE (within 30 days) was found to be 0.96%, with a positive association between length of surgery and VTE[29]. Interestingly, almost half of our VTE cohort (n=15, 41.7%) developed their events within 3 months post-surgery. Of these peri-operative cases, only 1 subject was over 65 (range of 16-75 years old) with a mean age of 49.7 years old, suggesting younger MEN1 patients undergoing surgery may also be at an increased risk of developing peri-operative VTE. Most of the cases of peri-operative VTE (7/15) were abdominal surgeries which are typically longer than parathyroid surgery. MEN1 patients often undergo multiple surgeries in their lifetime as resection is still the mainstay of treatment for hyperparathyroidism as well as for functional and/or metastatic pNETs and pNETs greater than 2 cm[1].

One study that evaluated the risk of VTE in patients with NETs (n=12/162; 7%) demonstrated increased thrombotic risk associated with pNETs (as compared to all gastroenteropancreatic NET), with higher risk in higher grade tumors[30]. Our data on tumor grade were insufficient to analyze for a correlation between NET grade and risk for VTE. Interestingly, in an evaluation of VTE incidence among abdominal NET surgical patients,

malignant pNETs had significantly higher (p=0.03) rates of developing post-operative VTE (defined as within 30 days) while benign pNETs were shown to have similar rates compared to those of other malignancies[31]. Taken together, these data may support prophylactic anti-coagulation therapy in patients with malignant and/or high grade pNETs.

Pedigree review demonstrated that multiple other MEN1 family members not enrolled in our protocol also developed a VTE. At least 3 VTE patients had undergone hematological evaluation due to family history of VTE without a known cause, and two patients had Factor V Leiden mutations. Only one previous case report of concomitant Factor V Leiden and MEN1 has been described[32], but there is no evidence to suggest that the *MEN1* locus (ch. 11q13) is linked with *F5* gene mutation (1q24.2).

While our study was limited in the ability to review primary data for patients who had events prior to enrollment at our institute (including available biochemical values at the time of event for those patients), data obtained from available records and from patients whose VTE event occurred during our study did not demonstrate any clear patterns to suggest causality. Evaluating our available biochemical and hematological data failed to yield a clear trend to identify biomarkers typical in pro-thrombolytic states[33]. Challenges in unraveling this increased VTE risk include deciphering whether the loss of function of the *MEN1* gene itself alone or in combination of the often concomitant endocrinopathies and multiple surgeries account for the increased incidence of VTE. In order to attempt to address this issue, we sought to compare with other MEN1 patients who have similar pathophysiology and treatment trajectories within the same cohort. Risks of bias include a lack of systematic collection of follow-up data, risk factor assessments between historical and present cohorts, and collection bias of data coming from a single institution. Additionally, we allow for the possibility of selection bias regarding the non-VTE sub-cohort. Per protocol, patients are invited for follow-up at our institution every 1-2 years. However, patients may elect to return

at varying intervals and those requiring close follow-up and/or intervention may present more frequently. These follow-up inconsistencies could have skewed our newly-implemented patient database, however, the scope and the range of clinical manifestations from this well-characterized cohort mimics other well-described long-standing MEN1 cohorts[1], with the caveat of all patients undergoing ^{68}Ga-Dotatate PET/CT scans, which may increase the sensitivity of detection of pNET diagnosis. A well-designed and controlled study is needed to determine which, if any, pro-coagulant and anti-thrombotic factors are contributing to increased VTE within the context of MEN1. It is also prudent to recognize that MEN1 tumor screening often begins with the first manifestation of disease or with genetic diagnosis[1], thus the patient-years in our cohort study would likely be significantly longer than patients who enter the medical system at the onset of disease (i.e., cancer or CS diagnosis). This may increase the number of person-years in our study, which we anticipate would be offset by our inclusion of larger studies with more patients.

CONCLUSIONS

Patients with cancer are known to have an increased risked to develop DVT or PEs around the time of and/or after cancer diagnosis. While MEN1 is comprised of multiple functional and non-functional NETs and hyperparathyroidism, it is not typically considered an active malignancy state as compared to other cancers, unless the NETs become malignant or high grade (which is rare). The paucity of data relating VTE and NET suggest that these tumors are not frequently associated with venous thrombosis. This is the first report describing VTE incidence and risk in MEN1. Our data demonstrate that MEN1 patients experience a two-fold increase in the incidence of VTE relative to the general population that is comparable to the risk associated with certain cancer types. Confirmation of this risk from

other MEN1 cohorts and patient populations with NETs is needed. Furthermore, thorough investigation of the pathophysiology and etiology of VTE in MEN1 is warranted. Patients and providers should be educated on the potential risk and symptoms of VTE in this population.

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DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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Table 1

	Non-VTE cohort	VTE cohort
Number of MEN1 patients (%)	83/278 (29.9)	36/278 (12.9)
Mean age (years; range)	46.9 (18-81)	46.4 (16-75)
Female (%)	35 (42)	18 (50)
Manifestations		
Pituitary adenoma diagnosis (%)	54 (65)	21 (58.3)
Size (mm)	7.5 ± 5.5	15.9 ± 17.8
Non-functional (%)	38 (70.4)	11 (52.4)
Prolactinoma (%)	13 (24.1)	9 (42.8)
TSH-secreting (%)	1 (1.9)	1 (4.76)
Pituitary surgery (%)	14 (16.9)	6 (28.6)
Hyperparathyroidism diagnosis (%)	81 (97.6)	36 (100)
PTH level (pg/mL; 15-65 pg/mL)	78.7 ± 105.5	73.7 ± 48.7*
Ionized calcium (mg/dL; 1.12- 1.32 mmol/L)	1.28 ± 0.12	1.35 ± 0.11*
Previous parathyroid surgery (%)	69 (83.1)	30 (83.3)
pNET diagnosis (%)	79 (95.2)	29 (80.1)
Non-functional (%)	73 (92.4)	22 (75.9)
Insulinoma (%)	4 (5.1)	7 (24.1)
Gastrinoma and/or Zollinger-Ellison diagnosis (%)	36 (43.3)	16 (44.4)

Gastrin level (pg/mL; 0-99 pg/mL)	636.2 ± 2446.1	685.6 ± 1807.6°
Metastatic neuroendocrine disease diagnosis (%)	28 (33.7)	7 (19.4)
Patients with MEN1-related abdominal surgeries prior to VTE (%)	38 (45.8)	18 (50)

Table 1. Demographic and MEN1 Characteristics. All biochemical values and tumor sizes expressed as mean ± standard deviation unless otherwise noted. For VTE cohort, MEN1 manifestations were recorded within ± 12 months of VTE event (n=36) and available biochemical values were recorded within ± 12 months for those who had a study-time event or available records (n=24 for PTH and ionized calcium, n=26 for gastrin). For non-VTE cohort, all MEN1 manifestations and biochemical values were evaluated within 2 years of time of analysis. For both cohorts, tumor functionality data are represented as fractions out of the number of patients with diagnosed tumors of the pituitary or pNETs. Abbreviations: MEN1, multiple endocrine neoplasia type 1; VTE, venous thromboembolism; TSH, thyroid stimulating hormone; pNET, pancreatic neuroendocrine tumor, PTH, parathyroid hormone; *, n=24; °, n=26

Figure 1

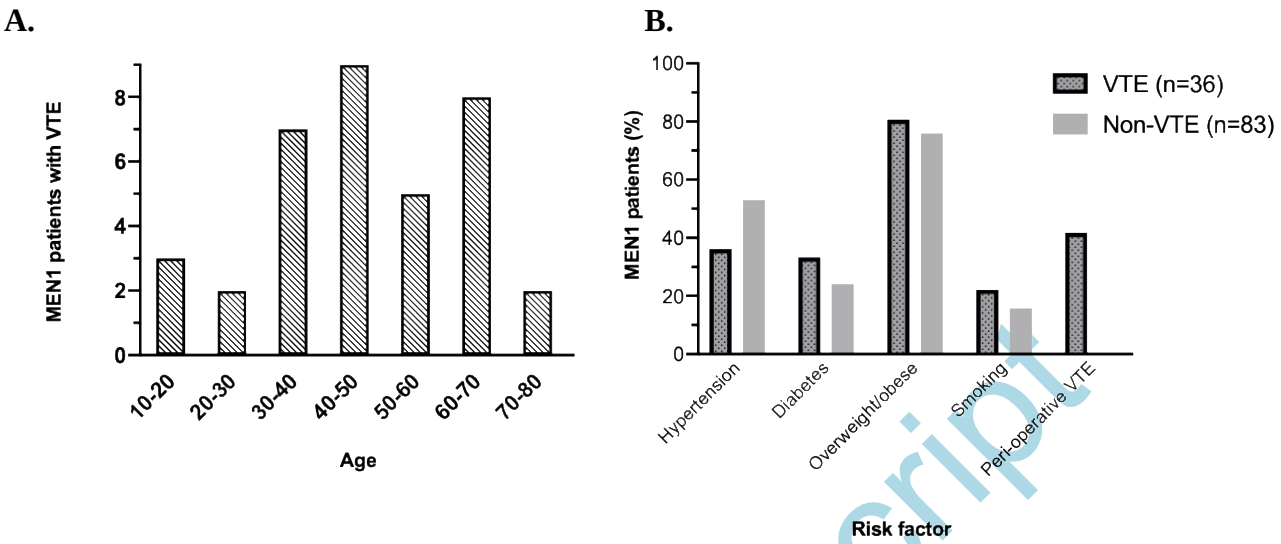

Figure 1. Risk factors for VTE among patients with MEN1. A) Age distribution of VTE events in patients with MEN1. Distribution of first lifetime VTE events by age within the MEN1 VTE cohort. **B) VTE risk factors in the MEN1 cohorts.** Documented risk factors of VTE within the MEN1 VTE and non-VTE cohorts shown as percent of total cohort. Hypertension was defined as per American Heart Association guidelines[14] >130/80 or the prescription of anti-hypertensive medications, type 2 diabetes mellitus defined as per American Diabetes Association guidelines[15], and overweight/obese diagnoses were calculated and defined as per the National Heart, Lung, and Blood Institute[34]. For VTE cohort only, peri-operative VTE defined as within 3 months prior to event, smoking history is self-reported. All values and/characteristics included in analysis were from within ± 12 months of VTE event. For the non-VTE cohort, data was either not applicable or not available for recent surgery, however smoking history was based on smoking status at time of analysis. Abbreviations: MEN1, multiple endocrine neoplasia type 1; VTE, venous thromboembolism

Figure 2

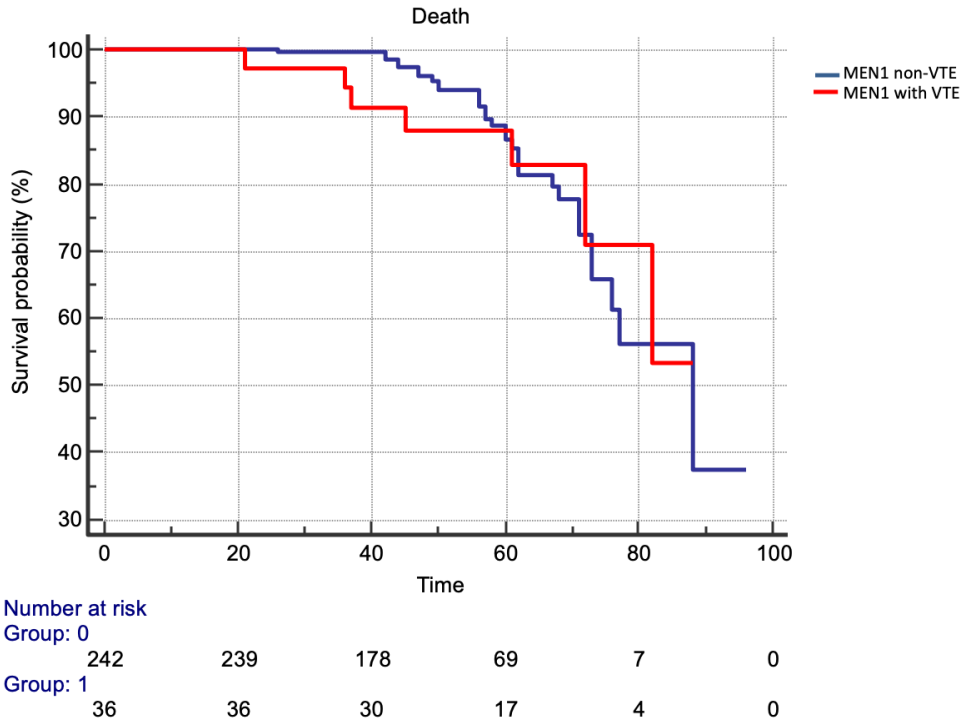

Figure 2. Kaplan-Meier Survival curves between VTE and non-VTE MEN1 cohorts. Comparison of survival between MEN1 patients who experienced at least one lifetime VTE (red) and MEN1 patients who have not (blue) demonstrating no significant difference. Abbreviations: VTE, venous thromboembolism

Figure 3

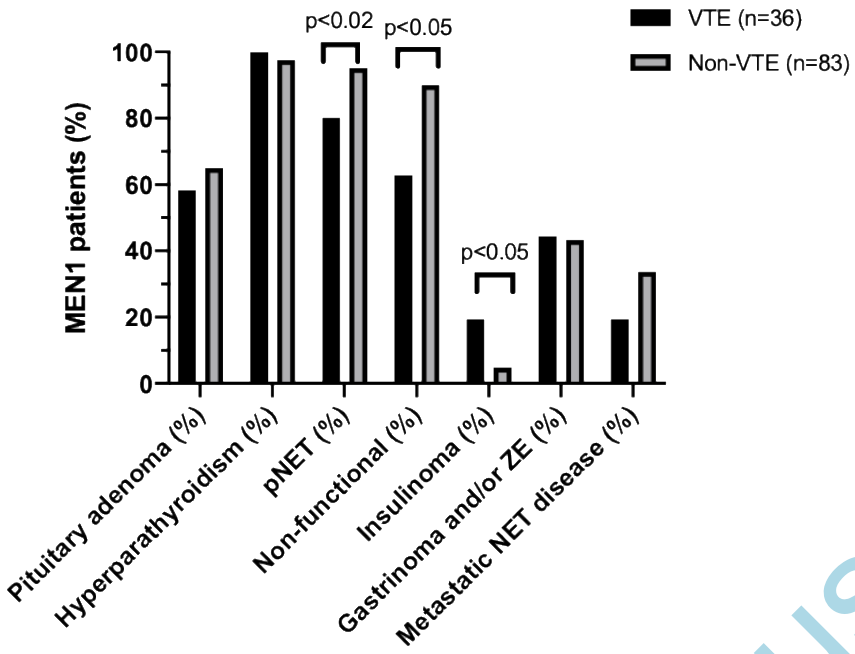

Figure 3. Comparative manifestations between VTE and non-VTE MEN1 cohort. Comparison of manifestations identified among MEN1 patients with and without VTE (as a percent of all subjects within each group). There are significant differences between the number of patients diagnosed with pNETs ($p<0.01$) within the entire VTE and non-VTE cohorts, including non-functional pNETs (n=22/35 vs 73/81, respectively; $p<0.05$) and insulinoma (n=7/36 vs 4/83, respectively; $p<0.05$). Abbreviations: MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; ZE, Zollinger-Ellison syndrome; VTE, venous thromboembolism

Table 2

Disease Process	Total VTE/person time (y)		IR per 1,000 p-y (95% CI)	
Cancer	*Gade I, et al. (2018)*	*Walker A, et al. (2013)*	*Gade (2018)*	*Walker (2013)*
All cancer types	110/30,021	3352/240,723	3.7 (3.1 - 4.5)	13.9 (13.4 - 14.4)
Breast	19/8,098	591/67,000	2.3 (1.5 - 3.7)	8.9 (8.2 - 9.6)
Prostate	18/4,619	383/42,000	3.9 (2.5 - 6.2)	9.1 (8.3 - 10)
Other solid tumors	40/10,506	n/a	3.8 (2.9 - 5.2)	n/a
Hematological (leukemia, etc.)	12/1,853	51/51,000	6.5 (3.7 - 11.4)	10 (7.6 - 13)
Control	321/165,180	6353/2,098,000	1.9 (1.7-2.2)	3 (3 - 3.1)
Cushing's Syndrome	*Dekkers O, et al. (2013)*			
3 years before diagnosis	n/a		4.3 (1.1 - 9.3)	
1 year after diagnosis	n/a		15.3 (4.9 - 31.4)	
>1 - 30 years after diagnosis	n/a		1.9 (0.8 - 3.6)	
Population Estimates	*Heit, et al. (2015)*			
European Ancestry	n/a		1.4 - 1.83	
Female (age-adjusted)	n/a		1.1	
Male (age-adjusted)	n/a		1.3	
MEN1 NIH Cohort				
Germline MEN1 (study-time VTE)	26/2,930		9.11 (1.8 – 4.6)	
Germline MEN1 (lifetime risk)	36/12,890		2.81 (1.8 – 4.4)	

Table 2. Incidence Rates Among Various Malignancies. Comparison of the reported incidence rates of VTE within various populations including cancer patients, Cushing's Syndrome patients, healthy people, and MEN1. Abbreviations: VTE, venous thromboembolism; IR, incidence rate; p-y, person-years; NIH, National Institutes of Health; Germline MEN1; germline *MEN1* mutation positive