Received: 12 February 2024 | Accepted: 11 March 2024

https://doi.org/10.1016/j.rpth.2024.102381

RESEARCH LETTER

Venous thromboembolism in pancreatic neuroendocrine neoplasm: a cohort study

KEYWORDS

neuroendocrine tumors, pancreatic carcinoma, pancreatic neoplasms, pulmonary embolism, thrombosis, venous thromboembolism

Neuroendocrine neoplasms represent a rare and heterogeneous group of malignancies originating from cells of the diffuse neuroendocrine system and may occur in multiple sites throughout the body, mainly in the gastroenteropancreatic tract [1]. Pancreatic neuroendocrine neoplasms could be classified into well-differentiated neuroendocrine tumors (PanNETs) and poorly differentiated neuroendocrine carcinomas based on their morphological features. Furthermore, PanNETs can be subdivided into low grade (G1), intermediate grade (G2), and high grade (G3) according to the Ki67 proliferation index, with the PanNET G3 group identifying highly proliferating well-differentiated tumors. In terms of prognosis, low-grade PanNETs tend to have a more indolent course, while high-grade PanNETs generally have a dismal prognosis, with overall survival (OS) rate like that of the adenocarcinoma counterpart [2].

In cancer patients, venous thromboembolism (VTE) occurs 9 times more frequently than in noncancer ones, and it is associated with increased mortality [3]. The development of VTE in the cancer population seems to be rising due to prolonged survival, more thrombogenic treatments, and higher awareness from physicians and patients [4]. VTE is prevalent in numerous malignancies, including pancreatic adenocarcinoma and gynecologic cancers [5]. Conversely, little is known about the specific thrombotic risk for pancreatic neuroendocrine neoplasms (PanNENs). Conversely, little is known about the specific thrombotic risk for a neoplasm originated from the pancreas [6]. Therefore, our aim was to identify VTE rates in the specific context of PanNENs and their impact on survival outcomes.

We conducted a retrospective study on patients with a histologically confirmed diagnosis of PanNET or poorly differentiated neuroendocrine carcinomas managed at the European Institute of Oncology from September 2018 to October 2021. Patient and tumor characteristics were collected at baseline and during follow-up. Information regarding VTE events (both symptomatic and incidental) including pulmonary embolism (segmental, subsegmental multiple, and isolated), deep vein thrombosis, and visceral vein thrombosis (VVT) was captured. VVT, defined as thrombosis of the splenic, hepatic, portal, mesenteric, renal, or ovarian veins, was included as potentially related to the disease. VTE was considered attributable to PanNENs if it occurred after neuroendocrine neoplasm diagnosis or within 30 days before the date of neuroendocrine neoplasm diagnosis. Data cutoff for survival analysis was September 30, 2022. The study was approved by an institutional review board on March 1, 2022 (UID-3009), and complied with the Strengthening the Reporting of Observational Studies in Epidemiology statement.

The incidence of VTE was reported as a rate per person-years using cumulative incidence function, estimated with the competing risk method, with death as a competing event. The Cox proportional hazards regression model for time to event was applied, and hazard ratio (HR) and 95% CI were reported. The occurrence of VTE was considered as a time-varying covariate. Comparison of relative risk was assessed by taking into account competing risks. This allowed the assessment of differences in associations using the Fine and Gray test. A landmark analysis for survival was performed, in which subjects who died within the landmark time (12 months from diagnosis) were excluded. All tests were performed 2-sided at a significance level of $\alpha = 0.05$. Statistics were performed using RStudio software version 2023.12.1+402.

The population included 248 patients, 48% female, with a median age at diagnosis of 52 years (IQR, 44-62 years). According to morphology, around 90% of cases were NETs, with 22% G1, 60% G2, and 18% G3. Seventy-five percent (187/248) had metastatic disease at the time of evaluation. The Supplementary Table summarizes baseline characteristics. At the data cutoff, 67% of patients were alive, whereas 33% had died, without any deaths recorded in patients without metastatic disease.

After PanNEN diagnosis, VTE occurred in 34 patients (13.7%) with a cumulative incidence of 3.84 (95% CI, 1.34-6.27) at 12 months, rising to 6.69 (95% CI, 3.19-10.07) and 8.96 (95% CI, 4.65-13.0) at 24 and 36 months, respectively. Isolated deep vein thrombosis was the most frequent presentation (50%), followed by VVT (29%) and pulmonary embolism (21%). The cumulative incidence of VTE was not statistically different for NET or neuroendocrine carcinoma (NEC) histology. However, when analyzed for high grade (NEC + NET G3) vs low grade (NET G1 + G2), cumulative VTE incidence after 1 year from diagnosis was statistically higher for low-grade PanNENs (Figure).

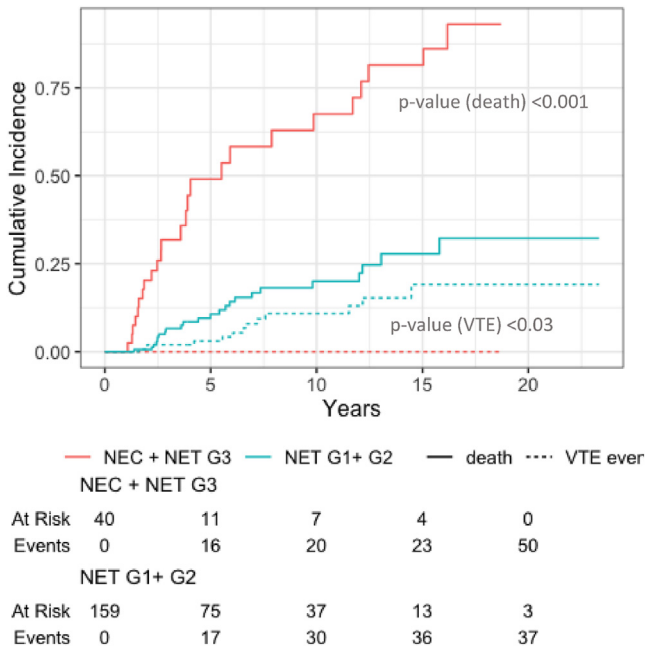

FIGURE Cumulative incidence of venous thromboembolism (VTE) and death (high grade vs low grade) after 12 months from diagnosis (time 0 is defined as the first year after diagnosis). G1, low grade; G2, intermediate grade; G3, high grade; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

After a median follow-up of 3.9 years (IQR, 2.5-8.6), the median OS for the entire population was 12.5 years (95% CI, 11.2-not reached), while median OS was 10.7 years (95% CI, 7.85-not available) in patients experiencing VTE and 15.0 years (95% CI, 12.1-not available) in patients without VTE. According to histology, median OS was statistically shorter in high-grade tumors than in low-grade tumors (2.66 years; [95% CI, 1.78-5.92] vs not reached; $P < .0001$). Applying the Cox proportional hazards regression model, VTE occurrence was statistically associated with poorer survival (HR, 2.84; 95% CI, 1.57-5.12; $P < .001$), and results were also confirmed at diagnosis excluding concomitant VTE (Table).

Limited to the NET subgroup, VTE was more frequent in patients with clinical syndrome (defined as functioning NET [F-NET]) compared with patients without clinical syndromes (defined as nonfunctioning NET [NF-NET]) (26% vs 13%; $P = .008$). The conditional cumulative incidence of death after 1 year from diagnosis was statistically higher for NF-NETs ($P = .05$), while the conditional cumulative incidence of VTE did not differ between NF-NETs and F-NETs ($P = .16$). Lastly, despite the wide estimates due to low numbers (27 patients), we observed an association with OS and VTE for the specific group of F-NETs.

The overall VTE rate in our retrospective study of PanNEN patients was around 14% over a median follow-up of 48.6 months, similar to other tumors with long survival in advanced settings [7]. Even though tumor aggressiveness represents a risk factor for VTE [4], in our population, we found a significant association between VTE occurrence and low-grade PanNENs. This result could be related to several aspects including the greater vascularization of low-grade NETs, the limited number of patients with NEC/NET G3, and a shorter OS for high-grade tumors, which compete with VTE risk. Provided that various factors may influence OS, our findings suggest that the occurrence of VTE may worsen survival and it should be carefully evaluated, especially in the context of long-lasting tumors. In terms of general prognosis, the impact of clinical syndrome on OS is not completely clarified, even though reports suggest a better survival for functioning tumors, especially insulinomas, potentially attributable to less biological aggressiveness and closer clinical monitoring [8]. Our results are consistent with that but, in this subgroup, the development of VTE seems to represent a detrimental factor for survival. Our study presents some limitations: the single-center and retrospective nature, the lack of biochemical parameters preventing risk stratification according to risk assessment models [9,10], and the absence of known concomitant anticoagulation that could have impaired the true incidence rate. Lastly, the small sample size in the F-NETs did not allow

TABLE Multivariable model (overall survival) with venous thromboembolism as a time-dependent variable in the overall sample and in the subgroup of patients without concomitant venous thromboembolism at diagnosis.

	Overall[a]				Removing patients with concomitant VTE diagnosis[b]			
Multivariable model	***N* = 240**	**HR**	**95% CI**	***P* value**	***N* = 230**	**HR**	**95% CI**	***P* value**
VTE event (time-dependent)								
No VTE	207	—	—		207	—	—	
VTE	33	2.84	1.57-5.12	<.001	23	4.78	2.26-10.1	<.001
Age		1.03	1.01-1.05	.002		1.03	1.01-1.05	.005
Type of NEN								
NEC + NET G3	60	—	—		56	—	—	
NET G1 + G2	180	0.16	0.10-0.25	<.001	174	0.14	0.09-0.23	<.001

G1, low grade; G2, intermediate grade; G3, high grade; HR, hazard ratio; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; VTE, venous thromboembolism.

[a]Eight observations were deleted due to missingness.

[b]Seven observations were deleted due to missingness.

definitive conclusions for the interpretation of HR estimates and results should be confirmed in a wider population. In conclusion, as far as we are aware, this is the first report to describe that VTE affects a relevant quote of PanNEN and may negatively impact OS, especially in the context of long-survival tumors. Moreover, F-NETs deserve further research as this could represent a subset at high risk of VTE, potentially leading to poorer outcomes.

ACKNOWLEDGMENTS

A special thanks to Dr Darina Tamayo, Dr Cristina Mazzon, and Dr Sabrina Boselli for their help in data management and the regulatory process. Thanks to all the patients and their families for their participation in the study.

FUNDING

The authors report no specific funding for leading this research.

ETHICS STATEMENT

This study was approved by an institutional review board on March 1, 2022 (UID-3009), and complied with the Strengthening the Reporting of Observational Studies in Epidemiology statement.

AUTHOR CONTRIBUTIONS

L.G. designed the study, collected data, interpreted data, and wrote the manuscript. A.L. collected data, interpreted data, and critically revised the intellectual content. L.B. and M.I.M.-M. collected data and critically revised the intellectual content. S.G. and A.G. analyzed and interpreted data and critically revised the intellectual content. M.R., C.A.C., L.B., M.B., L.A., G.C., and F.S. critically revised the intellectual content. N.F. interpreted data and critically revised the intellectual content.

RELATIONSHIP DISCLOSURE

N.F. reports public speaking for ADACAP and Ipsen and advisory board participation for ADACAP, Merck, Merck Sharp & Dohme, Novartis, Pfizer, and Boehringer. G.C. has received honoraria for speaker's engagement from Roche, Seagen, Novartis, Lilly, Pfizer, Bristol Myers Squibb, and Merck; honoraria for providing consultancy from Roche and Seagen; honoraria for participating in advisory board from Roche, Lilly, Pfizer, Foundation Medicine, Seagen, Novartis, Astra Zeneca, and Daichii Sankyo; honoraria for writing engagement from Novartis and Bristol Myers Squibb; honoraria for participation in Ellipsis Scientific Affairs Group; and institutional research funding for conducting phase I and II clinical trials from Pfizer, Roche, Novartis, Sanofi, Celgene, Servier, Orion, AstraZeneca, Seattle Genetics, AbbVie, Tesaro, Bristol Myers Squibb, Merck Serono, Merck Sharp Dome, Janssen-Cilag, Philogen, Bayer, Medivation, and MedImmune. F.S. reports public speaking and/or having a role as a consultant for Novartis, Ipsen, Advanced Accelerator Applications, Hutchmed, Merck Sharp & Dohme, and Merck. All other authors report no conflict of interest.

Lorenzo Gervaso[1,2]
Alice Laffi[3]
Aurora Gaeta[4]
Sara Gandini[4]
Laura Boldrini[5]
Monica Isabel Meneses-Medina[6]
Manila Rubino[1]
Lavinia Benini[1]
Michele Borghesani[1]
Laura Algeri[1]
Giuseppe Curigliano[5]
Francesca Spada[1]
Chiara Alessandra Cella[1]
Nicola Fazio[1]

[1]*Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, IRCCS, Milan, Italy*
[2]*Molecular Medicine Department, University of Pavia, Pavia, Italy*
[3]*Medical Oncology and Hematology Unit, Istituto Ricovero e Cura a Carattere Scientifico Humanitas Research Hospital, Rozzano, Milan, Italy*
[4]*Department of Experimental Oncology, European Institute of Oncology, IRCCS, Milan, Italy*
[5]*Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology, IRCCS, Milan, Italy*
[6]*Department of Hematology and Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*

Handling Editor: Dr Kristen Sanfilippo

Correspondence
Lorenzo Gervaso, Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, IRCCS, Via Ripamonti 435, 20141 Milan, Italy.
Email: Lorenzo.gervaso@ieo.it

Alice Laffi, Medical Oncology and Hematology Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy.
Email: Alice.laffi@humanitas.it

ORCID

Lorenzo Gervaso https://orcid.org/0000-0003-3313-8527

REFERENCES

[1] Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3:1335–42.
[2] Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76:182–8.

[3] Mulder FI, Horváth-Puhó E, van Es N, van Laarhoven HWM, Pedersen L, Moik F, et al. Venous thromboembolism in cancer patients: a population-based cohort study. *Blood*. 2021;137:1959–69.
[4] Gervaso L, Dave H, Khorana AA. Venous and arterial thromboembolism in patients with cancer: JACC: CardioOncology State-of-the-Art Review. *JACC CardioOncol*. 2021;3:173–90.
[5] Frere C, Bournet B, Gourgou S, Fraisse J, Canivet C, Connors JM, et al. Incidence of venous thromboembolism in patients with newly diagnosed pancreatic cancer and factors associated with outcomes. *Gastroenterology*. 2020;158:1346–58.e4.
[6] Massironi S, Cavalcoli F, Artoni A, Sciola V, Zilli A, Ciafardini C, et al. Thrombotic risk in gastroenteropancreatic neuroendocrine tumor patients: a single-center experience. *Ann Gastroenterol*. 2021;34:588–93.
[7] Gervaso L, Montero AJ, Jia X, Khorana AA. Venous thromboembolism in breast cancer patients receiving cyclin-dependent kinase inhibitors. *J Thromb Haemost*. 2020;18:162–8.
[8] Kasumova GG, Tabatabaie O, Eskander MF, Tadikonda A, Ng SC, Tseng JF. National rise of primary pancreatic carcinoid tumors: comparison to functional and nonfunctional pancreatic neuroendocrine tumors. *J Am Coll Surg*. 2017;224:1057–64.
[9] Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111:4902–7.
[10] Cella CA, Knoedler M, Hall M, Arcopinto M, Bagnardi V, Gervaso L, et al. Validation of the ONKOTEV risk prediction model for venous thromboembolism in outpatients with cancer. *JAMA Netw Open*. 2023;6:e230010. https://doi.org/10.1001/jamanetworkopen.2023.0010

SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2024.102381