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**Acute and Chronic Patients in the Emergency Department:
Characteristics of Patients Presenting with West Nile Virus Infection
and Cancer.**

Doctoral (Ph.D.) thesis

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1. Introduction

Emergency departments provide first-line care for patients admitted to inpatient care, thus operating as a "single-gate" system, regardless of the duration of the illness and the organ system involved. Due to this characteristic, the tasks of the emergency care staff include a wide spectrum of diseases: acute progression of chronic conditions, acute onset diseases, rare pathologies in addition to the most common diseases are all part of this spectrum.

In my personal experience, the challenge of emergency medicine is the application of an integrative approach that includes both the effective diagnosis and treatment of rare diseases as well as the management of the acute worsening of common chronic diseases requiring a multidisciplinary approach. This approach explains my choice of topic: the investigation of neuroinvasive infections caused by West Nile virus, which is a comparatively rare disease in Hungary, and the analysis of emergency department visits of cancer patients, which is a fairly common occurrence.

In Hungary, the number of West Nile virus infections increased significantly between 2014 and 2018, with a nearly eight-fold increase in 2018 compared to the previous year. Although 80% of West Nile virus (WNV) infections are asymptomatic, nearly 1% develop a neuroinvasive syndrome with high mortality and long-term complications. Therefore, it is important to identify high-risk patients early and to conduct research to identify new risk factors. Cancer is one of the leading causes of death worldwide, and in our country, mortality from cancer is especially high within the European Union. A significant proportion of patients with cancer visit emergency departments in the course of their illness, which place of care is often not optimal. Identifying the reasons for emergency care utilization is essential to organize optimized patient pathways and to reduce the burden on emergency departments.

2. Objectives

2.1 Concerning the research on „Identifying risks for severity of neurological symptoms in Hungarian West Nile virus patients”

The aim of our study was to analyze the neurological status of patients infected with West Nile virus at hospital admission and to assess the change in their condition over a short follow-up period using a known and a new neurological assessment method. We also aimed to identify potential risk factors of severe neurological outcome by collecting data on patients' demographic and clinical characteristics.

Research questions:

1. What was the incidence, severity, and duration of neurological symptoms in patients infected with West Nile virus in our country?
2. What demographic and clinical parameters influenced the odds of developing severe neurological symptoms?
3. Are there any previously unstudied parameters that influence the odds of developing severe neurological symptoms?
4. Is it possible to develop a tool that could potentially be used to measure the severity of neurological symptoms in patients with West Nile virus infection?

2.2 Concerning the research on „Main reasons and predictive factors of cancer-related emergency department visits”

The aim of this study was to investigate the association between clinical and demographic characteristics of cancer patients presenting to the emergency department and the reasons for emergency presentation. We also aimed to identify potential predictive factors of patients' emergency department visits that were due to the progression or complication of their cancer disease.

Research questions:

1. What are the most common reasons for patients with cancer to visit emergency departments?
2. What are the clinical characteristics of the patients who visit the emergency department due to the progression or complication of their cancer disease?
3. What are the clinical characteristics of patients with cancer who present to the emergency department for reasons unrelated to cancer?
4. What are the independent risk factors of a patient with cancer presenting to the emergency department due to the progression or complication of their cancer disease?

3. Methods

3.1 Concerning the research on „Identifying risks for severity of neurological symptoms in Hungarian West Nile virus patients”

We performed a retrospective study of adult patients with West Nile virus infection in four hospitals in Hungary over a 5-year period. In the course of data collection, we recorded a number of demographic and clinical parameters. Neurological status was assessed using the modified Rankin scale (mRS) and the WNV-N index (West Nile Virus Neurology Index) developed for this study, and patients were dichotomized into moderately severe and severe neurological status categories. Comparison of the presenting neurological status with the follow-up status, characterized by the mRS and WNV-N Index, were performed using the Wilcoxon Signed Ranks Test. To calculate the crude odds ratio for each risk as well as to determine the confounders and effect modifiers, stratified analysis was performed.

3.2 Concerning the research on „Main reasons and predictive factors of cancer-related emergency department visits”

The study was conducted in a level 3 emergency center, over a one-year study period, based on data from adult patients diagnosed with malignant neoplasms. In addition to collecting demographic and clinical data, we also categorized the reasons for emergency department visits, which we divided into 5 categories. Descriptive and exploratory approaches were used for statistical analysis. Predictive factors for patients with cancer visiting the emergency department were determined using binary logistic regression.

4. Results

4.1 Concerning the research on „Identifying risks for severity of neurological symptoms in Hungarian West Nile virus patients”

The demographic and general clinical characteristics of WNV patients:

A total of 66 patients with confirmed WNV infection were identified from four medical centers in Hungary within the five-year study period. The majority of the patients were male, and the average age of the patients was 56.74 years. The average number of days between the onset of neurological symptoms and hospital admission was 6.01 days, median 4.00. The most common general symptoms included fever (92.4%), weakness malaise/fatigue (39.4%), nausea/vomiting (39.4%), and skin rashes (30.3%).

Diagnostics, therapeutical interventions, and clinical outcomes of WNV patients:

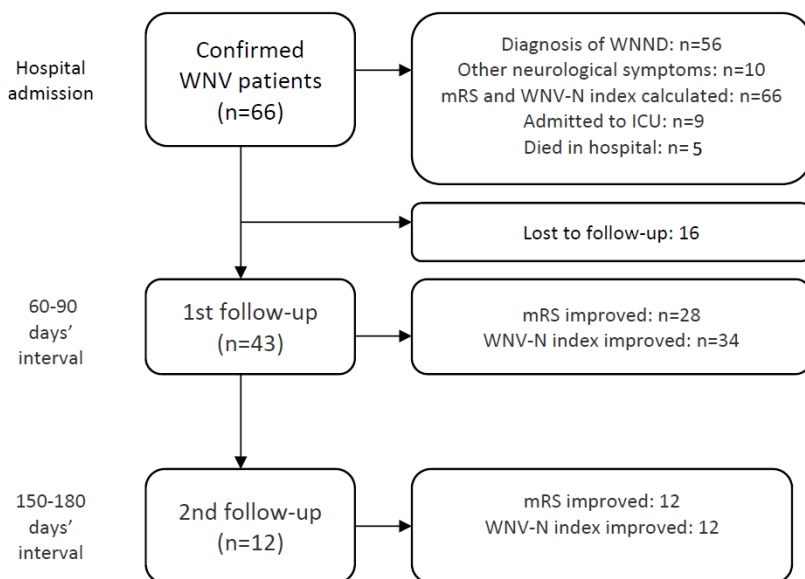
Cerebrospinal fluid (CSF) analysis was performed in most (72.7%) of the cases. IgA, IgG and IgM were positive in both the serum and CSF in the vast majority of the patients (93.9%). Polymerase chain reaction analysis showed positive results in a quarter of the patients (25.8%). Regarding treatment, almost half of the patients (48.5%) received both antiviral and antibiotic therapy, the majority (65.1%) received some form of pain medication and 9 patients (13.6%) required intensive therapy. The combination of mannitol and steroid (19.7%) and mannitol alone (13.64%) were the most frequently administered forms of additional medication. Complications during the hospital stay arose in almost one-fifth of the patients (18.2%) and 5 patients (7.57%) died.

Neurological symptoms and status upon hospital admission, and at the follow-up examinations:

All of the 66 patients' neurological examinations and assessments were carried out upon hospital admission. 43 patients were followed up within 60-90 days, and 12 patients within 150-180 days after

hospital discharge, which were defined as the 1st and 2nd follow-up appointments, respectively. 56 patients were diagnosed with WNND (West Nile neuroinvasive disease) but all of the 66 patients had some type of neurological symptom. None of the patients had meningitis, encephalitis, meningoencephalitis at the follow-up examinations. Based on their mRS categories, 27.3% of the patients' neurological status was considered severe following hospital admission. At the 1st follow-up only 14.0% were severe, and at the 2nd follow-up all patients were in the moderately severe category. According to our WNV-N Index, 33.3% of the patients had severe neurological status following hospital admission, which decreased to 14% and 8.3%, by the 1st and 2nd follow-up examinations, respectively. *Figure 1* shows the distribution of patients and process of investigation at hospital admission and follow-up.

Figure 1: Distribution of patients and process of investigation at hospital admission and follow-up



Risk factors for severe neurological status: We investigated whether risk factors for severe neurological status could be identified. Therefore, the associations between demographic and clinical features, based on the mRS and WNV-N index, were analyzed. Also, relationships between diagnostic and therapeutic interventions, occurrence of complications and severe neurological status were examined. *Table 1* shows the risk factors for severe neurological status.

Table 1: Risk factors for severe neurological status following hospital admission and/or at 1st follow-up, based on patients' mRS and WNV-N index

Risk factors	OR	95% CI
mRS (moderately severe/ severe neurological status)		
Age (<65 years / 65+ years) (N=66)	9.88	2.846 - 34.299
Comorbidities (2 or more) (no / yes) (N=66)	5.20	1.577 - 17.149
Weakness/malaise (no / yes) (N=66)	3.45	1.120 - 10.670
Complications (no / yes) (N=43)		--*
WNV-N Index (moderately severe/ severe neurological status)		
Complications (no / yes) (N=43)	6.50	1.130 – 37.200
Age (<65 years / 65+ years) (N=66)	4.91	1.628 – 14.817
Comorbidities (2 or more) (no / yes) (N=66)	4.59	1.530 – 13.778
Gait uncertainty (no / yes) (N=66)	3.75	1.126 – 11.123

* All patients with complications belonged to the „severe neurological status” category

The relationship between the severity of the neurological status and the time (in days) between the onset of neurological symptoms and hospital admission, were also analyzed. Our results showed that shorter time interval was a protective factor: the shorter the interval between the onset of symptoms and hospital admission, the greater the chance for patients to avoid severe neurological symptoms. This relationship is shown in *Table 2*.

Table 2: The relationship between the time (in days) between the onset of neurological symptoms and hospital admission and the severity of the neurological status following hospital admission based on patients' mRS scores and WNV-N Index scores

Based on mRS	B	S.E.	p-value	Exp (B)	95% CI
time between the onset of neurological symptoms and hospital admission	-0.374	0.133	0.005	0.688	0.530 – 0.894

$R^2 = 0.310$

Based on WNV-N Index	B	S.E.	p-value	Exp (B)	95% CI
time between the onset of neurological symptoms and hospital admission	-0.224	0.089	0.011	0.799	0.672 – 0.951

$R^2 = 0.211$

4.2 Concerning the research on „Main reasons and predictive factors of cancer-related emergency department visits”

Demographic and clinical characteristics of patients with cancer: In our study, we analyzed the demographic and clinical characteristics of emergency presentations of patients with cancer. We determined the five main reasons for emergency department (ED) visits: *cancer-related ED visit, oncological care-related ED visit, new cancer diagnosis-related ED visit, non-cancer related ED visit and undetermined ED visit* (Table 3).

Cancer-related ED visits resulted in the highest percentage of repeated ED visits. Except for *Oncological care-related ED visits*, all groups had a significantly higher proportion of patients over 65 years of age. ED visits were more frequent among females, with ED visits by males being significantly more frequent only among *undetermined* cases or among cases with a *new cancer diagnosis-related ED visit*. Patients with *non-cancer related ED visits* had the significantly highest proportion of ≥ 2 comorbidities, while patients with a *new cancer-related ED visit* had the lowest. Patients of

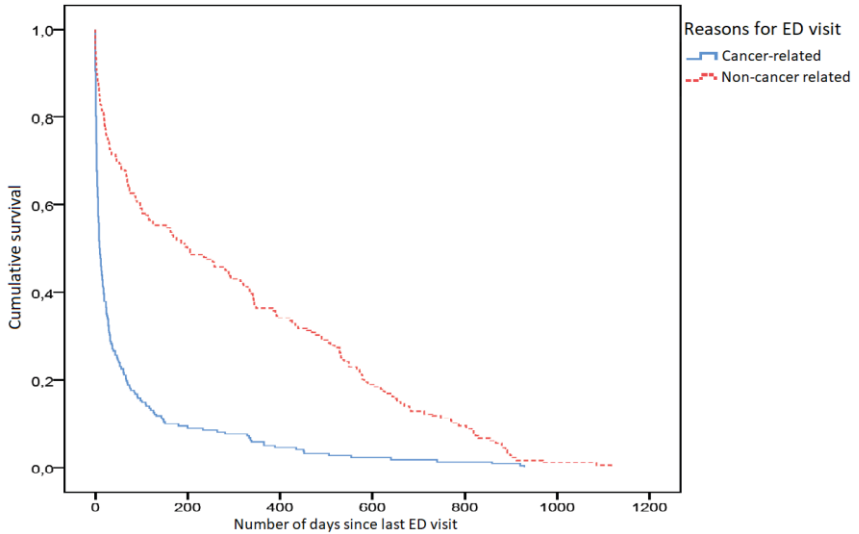
the latter group were given the highest proportion of the non-urgent triage category of 5, however the highest proportion of hospitalization was also observed in this category. Over three quarters of the cases of *Oncological care-related ED visits* received oncological treatment within 30 days of their ED presentation. The lowest hospitalization rate was found among those visiting for *non-cancer related* reasons. Overall mortality was the highest among patients admitted due to *cancer-related reasons* and lowest among patients with a *non-cancer related visit*.

Table 3: The definitions of the 5 main reasons for the ED visits of patients with cancer

Reason for ED visit	Definition
Cancer-related ED visit	Patients who visited the ER due to the complications or progression of their cancer disease.
Oncological care-related ED visit	Patients whose visit was due to the complications/adverse events of prior oncological therapy.
New cancer diagnosis-related ED visit	Cases where a strong suspicion of cancer arose at the given ER visit, which diagnosis was subsequently confirmed.
Non-cancer related ED visit	Patients whose visit to the ER was in no way associated with their cancer illness.
Undetermined ED visit	Patients whose medical condition could be a result of either the complication/progression of their cancer or due to completely other causes (e.g. lung cancer and COPD causing dyspnea)

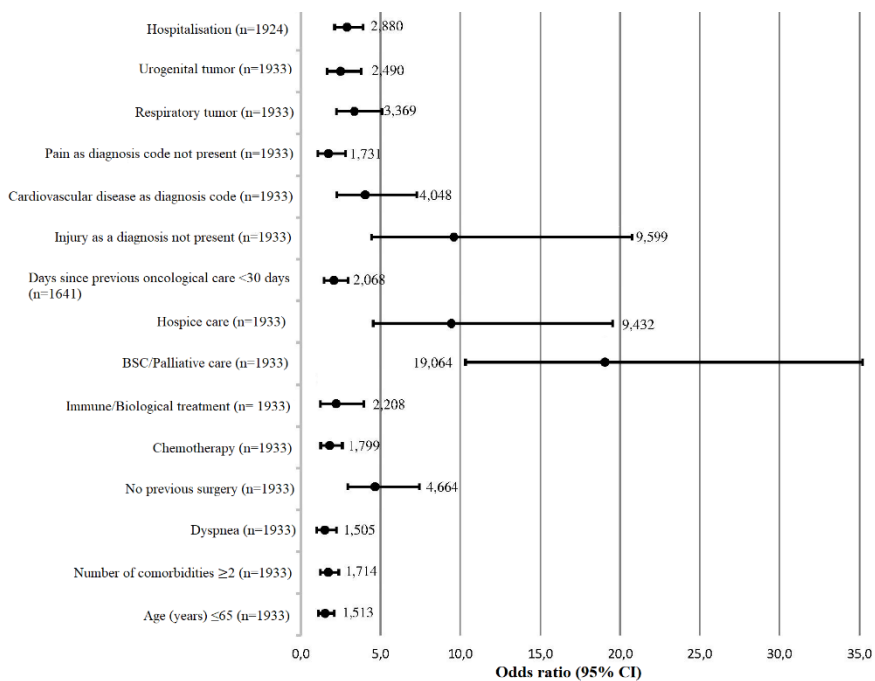
The 3-year survival of the above two groups was compared and is shown in *Figure 2*. Patients with *cancer-related visits* also had a significantly worse 30-day survival outcome than patients with *non-cancer related ED visits*.

Figure 2: 36-month overall survival of patients with visits related to cancer and non-cancer related reasons.



Predictive factors of cancer-related ED visits: We investigated whether predictors of cancer-related ED visits could be identified, therefore we analyzed the associations between the data of the two groups with the highest number of cases (*cancer-related (23.2%)* and *non-cancer related (58%)*). We identified a number of predictive factors that increased the odds that the *visit was cancer-related*. The independent risk factors for the cancer-related emergency department visits and the associated odds ratio values are illustrated in *Figure 3*.

Figure 3: Independent predictive factors of the ED visit happening due to cancer-related reasons



5. Discussion

Our study provided detailed data on the demographic and clinical characteristics of WNV infected patients from four regional medical centers in Hungary. Although PCR tests were positive in only 25.8% of cases - which could be explained by the short-term viremia and storage and shipment conditions - in all cases the infection was caused by the lineage-2 WNV strain, which was previously considered apathogenic, suggesting circulation of the strain in Hungary, in accordance with sequence data.

All 66 patients in the study had some type of neurological symptoms and 56 patients also developed neuroinvasive disease (meningitis, encephalitis, meningoencephalitis or acute flaccid paresis). Other frequent neurological symptoms found in our investigation were headache, vertigo and confusion following hospital admission which are in line with previous studies.

In previous studies, advanced age, immunosuppression, certain comorbidities have been shown to be associated with neuroinvasive infection and long-term neurological outcome. Accordingly, we found, that age >65 years and having ≥ 2 comorbidities, as well as certain presenting symptoms (“weakness/malaise” and gait uncertainty) significantly increased the odds of severe neurological status after hospital admission.

A recent study showed that admission to the intensive care unit predicted higher odds of in-hospital death and complications, such as inability to walk independently. Accordingly, in our study, the occurrence of complications significantly increased the odds of patients having a severe neurological status at 1st follow-up, underlining the importance of supportive care in WNND to prevent complications.

Only a few studies have reported the number of days between the onset of neurological symptoms and hospital admission, however, to our knowledge, none have investigated their association with neurological symptom severity.

Our most prominent finding, therefore, was that the longer the time between the onset of symptoms and hospital admission, the greater the patients' chances for having severe neurological status, thus shorter time intervals served as a protective factor.

Our findings regarding the above-described factors have several implications. It would be vital that patients with neurological symptoms present at their health care provider in time, as timely initiated supportive therapy could have a major impact on the patient's long-term prognosis.

As reported previously, WNV infection can be an occupational hazard, affecting the younger, active population. A recent investigation found that younger patients were more at risk of developing WNND, and age below 60 years was a predictor of intensive care unit admission. In our study, two-thirds of the patients were below 65 years, indicating that the young, active population, particularly with comorbidities, was also a high-risk population. Therefore, it appears important to implement appropriate epidemiological prevention measures and to provide information about the symptoms of WNV infection to the general population.

Assessment of risks and the use of evaluation scales help clinicians make timely decisions, especially in emergency settings where optimal allocation of resources is vital.

The WNV-N index developed for this study has the advantage of taking into account neurological symptoms specific to WNND. Based on our observations, the development and use of a validated assessment scale for patients presenting with symptoms suggestive of neuroinvasive disease may be worth considering.

In the second part of our research, we studied the emergency presentation of cancer patients, by investigating the clinical and demographic characteristics

of this patient group. We identified predictive factors of cancer-related presentations.

The proportion of patients with cancer visiting the ED in one year was 8.8% of the total visits made by adult patients in our study, which is in line with previous investigations that have reported ED visit rates between 1-12%. 21.4% of the patients with cancer required hospitalization. Compared to international data, where the hospitalization rates at the ED have been found to vary, between 12.4-58%, such as US (12.4%) and Australia (58%), our hospitalization rate was somewhere between these values. The observed differences between the countries are most probably due to the differences in distinct patient-routes of treatment and healthcare systems.

As in other studies, our results showed that the most common chief complaints, were pain, dyspnea and nausea or vomiting.

Our patients with cancer were mostly above 65 years of age, and the majority had ≥ 2 comorbidities, which is similar to previous reports that have found that older patients were more likely to visit the ED and to have three comorbid conditions on average.

Since we used a novel approach to categorizing the main reasons for ED visits, it is not possible to make direct comparisons with other studies, however, several previous investigations support our observations.

In a study which analyzed unplanned ED visits by patients receiving oncological treatment found that receiving anti-cancer therapy 28 days prior to ED presentation was independently related to increased ED utilization, which is in accordance with our findings about *oncological care-related ED visits*. Furthermore, 78.3% of our *oncological care-related ED cases* had received some form of treatment within 30 days of ED presentation, which also correlated with previous studies, which found high ED utilization ranging between 30-83% for patients having received chemotherapy.

Regarding cancer-related ED visits, one report found that patients who require palliative or hospice care are more likely to visit emergency departments, while another study found that 62.5% of cancer patients presenting to the emergency department had advanced metastatic cancers and the third most common ED diagnosis among patients with active cancer was “abnormality in breathing”. In line with these results, our cases with *cancer-related ED visits* had a high proportion of respiratory cancer cases, with chief complaint of dyspnea and ongoing BSC/palliative or hospice care.

A recent study in the US found that 11% of new cancer diagnoses were ED-mediated and that these patients were discovered to have had colorectal cancer in 13% of the cases. In accordance with previous data, our results showed that the proportion of *new cancer diagnosis-related ED visits* was 7.9%, and colorectal cancer was the most common type in our patients.

Visits of patients with cancer constitute a relevant proportion of all ED visits and while a part of these visits are related to the progression or previous treatment of cancer, a number of patients have medical conditions completely unrelated to their cancer illness and are nonurgent.

Allocating the required healthcare resources, may be aided by the awareness of the predictors of directly cancer-related conditions.

The burdens of ED healthcare staff would be alleviated and the quality of care for cancer patients could possibly be improved if medical conditions related to the progression of cancer or complications of oncological treatment could be managed within dedicated oncology units using dedicated patient pathways. Our present study can possibly provide a basis for the planning and implementing of such measures.

6. Theses

6.1. Concerning the research on „Identifying risks for severity of neurological symptoms in Hungarian West Nile virus patients”

1. The vast majority (85%) of WNV-infected patients we studied developed some form of WNND (meningitis, encephalitis, meningoencephalitis, or acute flaccid paralysis) and all patients had some neurological symptoms. Both the rate of neurological symptoms and the severity of the patient's condition had improved by the time of the follow-up visit between days 150 and 180.

2. Age over 65 years, ≥ 2 comorbidities, "weakness and malaise" and "gait uncertainty", and complications during hospital care significantly increased the odds of developing severe neurological status.

3. The interval between the onset of neurological symptoms and hospital admission influenced the severity of neurological symptoms in WNV-infected patients, and the shorter time interval was a protective factor against developing severe neurological symptoms.

4. We have developed the WNV-N index, a potential neurological status scale for WNV-infected patients, which in contrast to the mRS, takes into account the typical symptoms of WNV-associated neuroinvasive disease.

6.2. Concerning the research on „Main reasons and predictive factors of cancer-related emergency department visits ”

1. Emergency visits *due to the progression or complication of cancer disease* (23.2%) and *visits unrelated to cancer* (58%) accounted for the majority (81.2%) of all visits by cancer patients.

2. The group of emergency presentations *due to the progression or complication of cancer disease* had the highest proportion of repeated visits, accounting for 51.5% of emergency presentations. The most common leading complaint was dyspnea among cancer-related visits, and mortality within 30 days of care was proportionally highest in this patient group.

3. The highest rate of ≥ 2 comorbidities (66.7%) was in the group of cases with other causes *unrelated to cancer*. This category had the second highest proportion of non-urgent triage category 5 (30.8%). Less than a third (30.1%) of these patients required hospitalisation following emergency care. Mortality within 30 days of care was found to be lowest in this category (5.1%).

4. Age below 65 years (OR 1.51), dyspnoea as the chief complaint (OR 1.50), respiratory tumour, history of prior chemo- or immuno-/biological therapy, BSC/palliative (OR 19.06) or hospice care (OR 9.43), oncology care within 30 days, need for hospitalisation and certain diagnoses (cardiovascular disease), or lack of diagnoses (injury related diagnosis or pain) significantly increased the odds that the visit *was due to progression or complication of cancer disease*. They were independent risk factors for the emergency department visit to be cancer-related.

7. Conclusions

The primary challenge of emergency medicine is the application of an integrative approach that includes both the management of the acute worsening of common chronic diseases as well as the effective diagnosis and treatment of rare diseases. This choice of two research areas - a study on neuroinvasive disease caused by West Nile virus and an investigation of the emergency presentations of cancer patients – represents the dual challenge of emergency medicine.

We conducted our study on a cohort of patients treated for neuroinvasive WNV infection, which has increased dramatically in recent years in Hungary. Old age, comorbidities, complications significantly increased the risk of developing severe neurological symptoms, both during hospital stay and follow-up. We identified a new risk factor for more severe neurological outcome, the longer time between the onset of neurological symptoms and hospital admission. Our results suggest that vigilance regarding WNV infection needs to be increased among both the general population and clinicians, and the development of a neurological assessment scale for neuroinvasive infections may be important to improve disease outcome.

In our study of patients with cancer presenting to the emergency department, we used a novel approach to identify independent predictive factors of emergency department presentations based on the chief cause of their visit. We showed that about a quarter of the studied patients presented due to progression of cancer disease, and that the survival of these patients was significantly worse than other cancer patients'. We also identified several risk factors for cancer-related visits. Our results may provide important information for the development of algorithms for the care of patients with cancer and may also provide an opportunity for early identification of high-risk patient groups as well as the organization of alternative patient pathways.

8. Publications

8.1 Publications related to the topic of the thesis and on which the thesis is based:

Koch M, Pozsgai É, Soós V, Nagy A, Girán J, Nyisztor N, Martyin T, Müller Z, Fehér M, Hajdú E, Varga C. Identifying risks for severity of neurological symptoms in Hungarian West Nile virus patients. *BMC Infect Dis.* 2021 Jan 13;21(1):65. doi: 10.1186/s12879-020-05760-7. PMID: 33441090; PMCID: PMC7805165.

Q2, IF: 3.669

Koch M, Varga C, Soós V, Prenek L, Porcsa L, Szakáll A, Bilics G, Hunka B, Bellyei S, Girán J, Kiss I, Pozsgai É. Main reasons and predictive factors of cancer-related emergency department visits in a Hungarian tertiary care center. *BMC Emerg Med.* 2022 Jun 23;22(1):114. doi: 10.1186/s12873-022-00670-0. PMID: 35739467; PMCID: PMC9219147.

Q1, IF: 2.485

Other publications (other than those on which the thesis is based) related to the topic of the thesis:

Koch M, Török KT, Nagy F, Soós V, Pozsgai É, Lelovics Z, Nagy A, Varga C. A nyugat-nílusi vírus okozta neuroinvaszív tünetegyüttes előfordulása sürgősségi osztályon [The occurrence of neuroinvasive symptoms caused by the West Nile virus at an emergency center]. *Orv Hetil.* 2019 Dec;160(51):2026-2035. Hungarian. doi: 10.1556/650.2019.31575. PMID: 31838862.

Q4, IF: 0.707

Koch M*, Szabó É*, Varga C, Soós V, Prenek L, Porcsa L, Bellyei S, Girán K, Girán J, Kiss I, Pozsgai É. Retrospective study of cancer patients' predictive factors of care in a large, Hungarian tertiary care centre. *BMJ Open*. 2023 May 8;13(5):e070320. doi: 10.1136/bmjopen-2022-070320. PMID: 37156589; PMCID: PMC10174014.

*Shared first authorship

Q1, IF: 3.007

Total (first author) impact factor associated with the thesis: 9.868

8.2 Other publications not related to the thesis:

Varga C, Kálmán Z, Szakáll A, Drubits K, **Koch M**, Bánhegyi R, Oláh T, Pozsgai É, Fülöp N, Betlehem J. ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic patients. *BMC Emerg Med*. 2019 May 31;19(1):33. doi: 10.1186/s12873-019-0247-0. PMID: 31151388; PMCID: PMC6814982.

Q1, IF: 2.485

Total impact factor of all publications: 12.353

8.3 Presentations related to the topic of the thesis

„A daganatos betegek sürgősségi osztályon történő megjelenését előrejelző tényezők” („Predictors of cancer patients presenting to the emergency department”)

(XX. Hungarian Congress of Emergency Medicine, Siófok, Nov. 06, 2021)

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