clinical and translational neuroscience

MDPI

Article

Sex Differences in Ischemic Cerebral Infarction: A Nationwide German Real-Life Analysis from 2014 to 2019

Claudia Lappe [1,*], Holger Reinecke [1,*], Jannik Feld [2] and Jeanette Köppe [2]

[1] Department of Cardiology I—Coronary and Peripheral Vascular Disease, Heart Failure, University Hospital Muenster, 48149 Muenster, Germany
[2] Institute of Biostatistics and Clinical Research, University of Muenster, 48149 Muenster, Germany
* Correspondence: clappe@uni-muenster.de (C.L.); holger.reinecke@ukmuenster.de (H.R.)

Abstract: Female sex has been shown to be associated with an unfavorable outcome after ischemic stroke. In this nationwide analysis, we evaluate a large dataset of patients suffering from acute ischemic stroke to elucidate the factors associated with an increased risk of mortality after stroke in women. We analyzed a nationwide dataset from the German Federal Bureau of Statistics including 1,577,884 (761,537 female sex, 48.3%) in-hospital cases admitted between 1 January 2014 and 31 December 2019 with a primary diagnosis of acute ischemic cerebral infarction. Patients were analyzed regarding morbidity, treatments and in-hospital mortality. A multiple logistic regression analysis was performed, adjusted by patients' risk profile including age, to evaluate the association of sex and in-hospital mortality. According to the median, women were older than men (79 years vs. 73 years). The multiple logistic regression analysis however revealed female sex remained an independent factor for an increased in-hospital mortality (odds ratio [OR] 1.12; 95% confidence interval [CI] 1.11–1.14; $p < 0.001$). Women had a higher prevalence of relevant risk factors, namely arterial hypertension (77.0% vs. 74.7%), arterial fibrillation (33.3% vs. 25.6%), chronic heart failure (12.3% vs. 9.7%), chronic kidney disease (15.6% vs. 12.9%) and dementia (6.6% vs. 4.1%), but were less affected with respect to other relevant co-morbidities such as cerebrovascular disease (11.7% vs. 15.1%), coronary heart disease (11.7% vs. 18.8%), diabetes mellitus (26.4% vs. 29.6%), dyslipidemia (38.1% vs. 42.0%), ischemic heart disease (12.3% vs. 19.3%) and previous coronary artery bypass grafting (1.1% vs. 3.2%). Overall, therapeutic interventions were performed less frequently in women such as carotid endarterectomy (1.1% vs. 2.3%), carotid stent (0.7% vs. 1.4%), as well as hematoma drainage (0.1% vs. 0.2%), and renal replacement therapy (0.4% vs. 0.6%). Conclusions: Our nationwide analysis revealed a higher mortality rate after stroke in women. Nevertheless, women had fewer in-hospital complications and were also less likely to experience the severe effects of some important co-morbidities. The dataset, however, showed that women received surgical or interventional carotid treatments after stroke less often. It is important for research on sex disparities in stroke to keep these treatment frequency differences in mind.

Keywords: sex differences; ischemic cerebral infarction; in-hospital mortality

Citation: Lappe, C.; Reinecke, H.; Feld, J.; Köppe, J. Sex Differences in Ischemic Cerebral Infarction: A Nationwide German Real-Life Analysis from 2014 to 2019. *Clin. Transl. Neurosci.* **2022**, *6*, 23. https://doi.org/10.3390/ctn6030023

Academic Editor: Susanne Wegener

Received: 21 May 2022
Accepted: 7 September 2022
Published: 12 September 2022

1. Introduction

Stroke is a major cause of death and a leading cause of severe and long-lasting disabilities worldwide. Women are more at risk of being affected by stroke than men, and women are more likely to die or become severely disabled as a result of a stroke [1,2]. Stroke risk increases with age, and the unequal distribution in mortality can also be explained by women's increased longevity and the older age of women at stroke occurrence. However, several studies suggest that sex-specific differences in stroke care might also contribute to the higher frequency of negative clinical outcomes in women [1,3]. These studies indicate that several routine stroke investigations are performed less frequently in women as compared to age-adjusted men [3]. Thus, women are less likely to receive,

for example, acute revascularization therapies [4–6], brain imaging, echocardiograms and angiography than age-adjusted men [2]. Additionally, women, as compared to men, show more generalized, non-traditional symptoms, such as general weakness, disorientation, headache and changes in consciousness [2,7]. These atypical symptom presentations could lead to a delay in stroke diagnosis, decreasing the chances of a positive outcome [7]. Other possible reasons that could explain a less favorable outcome after stroke in women include differences in risk factor and stroke profile [2], disparities regarding therapy response, and stroke severity [3,8], as well as factors such as marital status and door to needle time [6].

Stroke registries can make an important contribution to identify sex specific differences regarding symptoms, co-morbidities and clinical outcome after a stroke [9]. Here, we analyzed sex differences in stroke data provided by the Federal Statistical Office (Statistisches Bundesamt (DESTATIS) containing in-patient care and in-hospital outcome of ischemic stroke cases. Patient characteristics including coexisting co-morbidities and other additional risk factors were analyzed to investigate further whether sex-specific factors can explain the increased stroke mortality rate in women.

2. Materials and Methods

The German remuneration system requires the coding of a main diagnosis for all in-hospital cases. There is an obligation that the reason for hospitalization is clear from the principal diagnosis. In addition, an unlimited number of additional diagnoses can be included in order to document coexisting morbidities as well as complications. The diagnoses have to be coded in accordance with the German Modification of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10-GM). Diagnostic, endovascular, and surgical procedures are coded in detail according to the German Procedure Classification (OPS). Diagnoses and procedures assigned to the respective ICD/OPS codes used in this analysis are listed in Supplementary Tables S1 and S2.

Due to federal law, all German hospitals have been required to transfer the collected data on all in-hospitalizations to the National Institute for Hospital Remuneration (Institut für das Entgeltsystem im Krankenhaus, InEK; Siegburg, Germany) since 2002. Thanks to the Federal Statistical Office, these large data records are available after 2 years for scientific purposes.

The database provided by the Federal Statistical Office contains all in-patient treated patients on a case basis per year, except for treatments in psychiatric or psychosomatic units. There was only remote access to anonymous data.

2.1. Patients

We identified all cases with a main diagnosis of acute ischemic stroke between 1 January 2014 and 31 December 2019, by the use of ICD code I63 or I64 as the main diagnosis. Furthermore, data on concomitant diseases, risk constellations and selected cardiovascular procedures were acquired for sex-specific analysis. Further details have been described previously [10].

2.2. Statistics

The analysis covers all in-patient ischemic stroke cases in Germany and does not represent a subsample. With regard to the primary question of this work, we wanted to address differences between female and male patients based on in-hospital mortality and differences between both sexes in the association of different factors for in-hospital deaths with acute ischemic stroke.

Furthermore, we wanted to address various in-hospital treatment strategies between female and male sex. Relative frequencies of death, in-hospital outcomes, coronary intervention or surgery were tested via a two-sided Chi-square test. Multivariable logistic regression analysis for in-hospital mortality was performed to evaluate the association of sex and in-hospital death adjusted by the patient's risk profile including age, diabetes mellitus, chronic heart failure, chronic kidney disease, peripheral arterial disease, atrial

fibrillation and/or flutter, hypertension, previous stroke, dyslipidemia, obesity, smoking and cancer. In order to address different patients' risk profiles between female and male sex, we evaluated the interaction of sex with all other variables in a second model. Odds ratios (OR), 95% confidence intervals (CIs) and p-values for all variables in the subgroups are shown in Supplemental Tables S3 and S4. Inferential statistics were intended to be exploratory (hypotheses generating), not confirmatory, and were interpreted accordingly. Statistical analyses were performed using SAS software V9.4, SAS Institute Inc., Cary, NC, USA and R version 4.1.0, R foundation, Vienna, Austria.

3. Results

In total, we investigated the data of 1,577,884 (761,537 female sex, 48.3%) cases with a primary diagnosis of acute ischemic cerebral infarction (Table 1).

Table 1. Baseline characteristics of patients hospitalized with ischemic stroke from 2014 to 2019.

	Male Sex	Female Sex	Total	*p* Value
Number of cases—*n* (%)	816,347 (51.7)	761,537 (48.3)	1,577,884 (100.0)	n.a.
Median age—Yr (Q1,Q3)	73 (63,80)	79 (70,85)	76 (66,83)	<0.001
Co-Diagnosis				
LEAD Stages—*n* (%):				
LEAD RF 1–3	20,585 (2.5)	11,035 (1.5)	31,620 (2.0)	<0.001
LEAD RF 4–6	8502 (1.0)	5730 (0.8)	14,232 (0.9)	
Arterial hypertension—*n* (%)	610,053 (74.7)	586,667 (77.0)	1,196,720 (75.8)	<0.001
Atrial fibrillation and/or flutter—*n* (%)	208,734 (25.6)	253,865 (33.3)	462,599 (29.3)	<0.001
Acute myocardial infarction—*n* (%)	10,392 (1.3)	9493 (1.3)	19,885 (1.3)	0.137
Cancer—*n* (%)	25,631 (3.1)	19,353 (2.5)	44,984 (2.9)	<0.001
Cerebrovascular disease—*n* (%)	123,392 (15.1)	89,418 (11.7)	212,810 (13.5)	<0.001
Coronary heart disease—*n* (%)	153,713 (18.8)	88,768 (11.7)	242,481 (15.4)	<0.001
Chronic heart failure—*n* (%)	79,261 (9.7)	93,264 (12.3)	172,525 (10.9)	<0.001
RV-CHF—*n* (%)	15,958 (2.0)	21,624 (2.8)	37,582 (2.4)	<0.001
LV-CHF—*n* (%)				
NYHA I	7486 (0.9)	7367 (1.0)	14,853 (0.9)	<0.001
NYHA II	19,090 (2.3)	22,237 (2.9)	41,327 (2.2)	
NYHA III	19,331 (2.4)	22,219 (2.9)	41,550 (2.6)	
NYHA IV	14,012 (1.7)	16,241 (2.1)	30,253 (1.9)	
Chronic kidney disease—*n* (%)	105,035 (12.9)	118,463 (15.6)	223,498 (14.2)	<0.001
Diabetes mellitus—*n* (%)	241,587 (29.6)	200,635 (26.4)	442,222 (28.0)	<0.001
Dyslipidemia—*n* (%)	343,071 (42.0)	290,487 (38.1)	633,558 (40.2)	
Obesity—*n* (%)	38,809 (4.8)	37,922 (5.0)	76,731 (4.9)	<0.001
Current smoking—*n* (%)	49,429 (6.1)	21,128 (2.8)	70,557 (4.5)	<0.001
Prev. Ischemic stroke—*n* (%)	61,288 (7.5)	49,590 (6.5)	110,878 (7.0)	<0.001
Prev. Intracranial bleeding—*n* (%)	4421 (0.5)	3589 (0.5)	8010 (0.5)	<0.001
Ischemic heart disease—*n* (%)	157,713 (19.3)	93,694 (12.3)	251,407 (15.9)	<0.001
Dementia—*n* (%)	33,086 (4.1)	50,080 (6.6)	83,166 (5.3)	<0.001
Prev. CABG—*n* (%)	25,930 (3.2)	8663 (1.1)	34,593 (2.2)	<0.001
Prev. Valve replacement—*n* (%)	6701 (0.8)	4400 (0.6)	11,101 (0.7)	<0.001

n.a. denotes not applicable; LEAD—lower extremity arterial disease; RF—Rutherford; RV-CHF—right ventricular chronic heart failure; LV-CHF—left ventricular chronic heart failure; NYHA—New York Heart Association; CABG—coronary artery bypass grafting; Yr—year; prev.—previous.

Key baseline characteristics of patients (Table 1) showed that women, as compared with men, were generally older at stroke onset (median (interquartile range): 79 (15) vs. 73 (17)). Women also showed a higher incidence of relevant co-morbidities, namely arterial hypertension (77.0% in women vs. 74.7% in men), arterial fibrillation (33.3% vs. 25.6%), chronic heart failure (12.3% vs. 9.7%), chronic kidney disease (15.6% vs. 12.9%) and dementia (6.6% vs. 4.1%). On the other hand, women were less affected than men with respect to other relevant co-morbidities such as cerebrovascular disease (11.7% in women vs. 15.1% in men), coronary heart disease (11.7% vs. 18.8%), diabetes mellitus (26.4% vs.

29.6%), dyslipidemia (38.1% vs. 42.0%), ischemic heart disease (12.3% vs. 19.3%) and previous coronary artery bypass grafting (CABG; 1.1% vs. 3.2%).

With respect to therapeutic interventions, fewer stroke routine treatments were carried out in women (Table 2). For example, carotid interventions were performed less frequently in women (carotid endarterectomy (EA): 1.1% in women vs. 2.3% in men; carotid stent: 0.7% vs. 1.4%), as well as hematoma drainage (0.1% vs. 0.2%), percutaneous coronary intervention (PCI; 0.2% vs. 0.4%) and renal replacement therapy (0.4% vs. 0.6%).

Table 2. In-patient treatment and complications. Ischemic cerebral infarction female vs. male sex from 2014 to 2019.

	Male Sex	Female Sex	Total	*p* Value
Carotid EA—*n* (%)	18,496 (2.3)	8601 (1.1)	27,097 (1.7)	<0.001
Carotid stent—*n* (%)	11,353 (1.4)	5126 (0.7)	16,479 (1.0)	<0.001
Carotid Interposition graft *n* (%)	162 (0.0)	59 (0.0)	221 (0.0)	<0.001
Decompressive hemicraniectomy—*n* (%)	3121 (0.4)	2563 (0.3)	5684 (0.4)	<0.001
Evacuation of extracranial hemorrhage—*n* (%)	1504 (0.2)	915 (0.1)	2419 (0.2)	<0.001
Evacuation of ICH—*n* (%)	17 (0.0)	15 (0.0)	32 (0.0)	0.875
Thrombectomy extra/intra cranial	30,905 (3.8)	34,919 (4.6)	65,824 (4.2)	<0.001
PCI—*n* (%)	3378 (0.4)	1707 (0.2)	5085 (0.3)	<0.001
DES—*n* (%)	2419 (0.3)	1147 (0.2)	3566 (0.2)	<0.001
BMS, only—*n* (%)	211 (0.0)	108 (0.0)	319 (0.0)	
CABG—*n* (%)	88 (0.0)	25 (0.0)	113 (0.0)	<0.001
Renal replacement therapy—*n* (%)	4937 (0.6)	3126 (0.4)	8063 (0.5)	<0.001
Systemic thrombolysis—*n* (%)	106,291 (13.0)	97,864 (12.9)	204,155 (12.9)	<0.002
Selective thrombolysis—*n* (%)	2737 (0.3)	2688 (0.4)	5425 (0.3)	0.058
Intra-arterial thrombolysis—*n* (%)	193 (0.0)	139 (0.0)	332 (0.0)	0.020
GpIIb/IIIa inhibitor—*n* (%)	1352 (0.2)	823 (0.1)	2175 (0.1)	<0.001
Hemorrhagic transformation—*n* (%)	27,715 (3.4)	26,977 (3.5)	54,692 (3.5)	<0.001
Bleeding—*n* (%)	12,558 (1.5)	10,899 (1.4)	23,457 (1.5)	<0.001
Blood transfusion—*n* (%)	15,389 (1.9)	17,321 (2.3)	32,710 (2.1)	<0.001
Blood transfusion or bleeding event—*n* (%)	25,094 (3.1)	25,406 (3.3)	50,500 (3.2)	<0.001
AKI—*n* (%)	18,580 (2.3)	15,661 (2.1)	34,241 (2.2)	<0.001
Sepsis—*n* (%)	12,927 (1.6)	8251 (1.1)	21,178 (1.3)	<0.001
AKI or need for dialysis—*n* (%)	21,849 (2.7)	17,931 (2.4)	39,780 (2.5)	<0.001
Cardiac arrest—*n* (%)	4742 (0.6)	3354 (0.4)	8096 (0.5)	<0.001
Mechanical ventilation—*n* (%)	43,385 (5.3)	35,996 (4.7)	79,381 (5.0)	<0.001
Median duration of ventilation—h (IQR)	115 (308)	72 (242)	93 (280)	<0.001
In-Hospital Death—*n* (%)	44,518 (5.5)	61,489 (8.1)	106,007 (6.7)	<0.001
Mean length of hospital stay—days (SD)	12.0 (14.3)	12.1 (12.7)	12.0 (13.5)	<0.001
Mean charges per case—EUR (SD)	7145.00 (10,816.93)	6733.49 (8858.98)	6946.17 (9921.42)	<0.001

EA denotes endarterectomy; ICH—intracerebral hemorrhage; PCI—percutaneous coronary intervention; DES—drug-eluting stent; BMS—bare-metal stent; CABG—coronary artery bypass grafting; Glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors; AKI—acute kidney injury; h—hours; IQR—interquartile range; SD—standard deviation.

With regard to in-hospital complications (Figure 1), ventilation treatment differed in women and men, revealing a lower treatment frequency (4.7% vs. 5.3%) and duration (72 h vs. 115 h) in women. Women were also less likely to be resuscitated (0.4% vs. 0.6%) and to develop sepsis (1.1% vs. 1.6%), but received, on the other hand, blood transfusion more frequently (2.3% vs. 1.9%).

In-Hospital Mortality

In absolute terms, in-hospital mortality in women suffering from an acute ischemic cerebral infarction was higher compared to men, with 61,489 (8.1%) vs. 44,518 (5.5%) ($p < 0.001$) (Table 2).

Adjustment for patient risk profile including age, using a multivariate logistic regression analysis, revealed female sex to remain an independent factor for an increased in-hospital mortality (OR 1.12; 95% CI 1.11–1.14; $p < 0.001$, Figure 2). Furthermore, in-

hospital mortality was highly affected by patients' co-morbidities. The results revealed that chronic heart failure as a secondary diagnosis was associated with an increased mortality rate in both women and men, but the risk for men was higher as compared to women (OR 1.63; 95% Cl 1.59–1.67 vs. OR 2.10; 95% Cl 2.04–2.15). This also applied to cancer as a secondary diagnosis (OR 2.11; 95% Cl 2.02–2.20 vs. OR 2.52; 95% Cl 2.43–2.62). Men also had a higher risk of dying when a stroke was accompanied by a chronic kidney disease (OR 1.01; 95% Cl 0.99–1.03 vs. OR 1.17; 95% Cl 1.14–1.20), or when suffering from atrial fibrillation and/or flutter (OR 1.34; 95% Cl 1.31–1.36 in women vs. OR 1.38; 95% Cl 1.35–1.41 in men; $p = 0.040$).

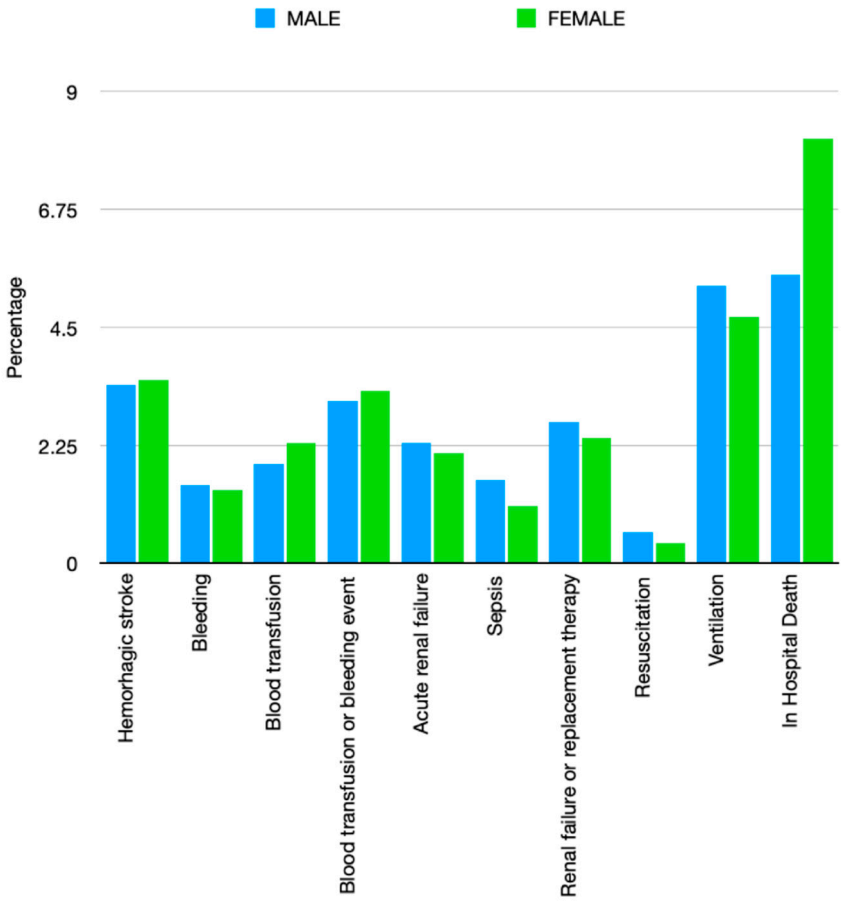

Figure 1. In-patient hospital complication and mortality rate female sex versus male sex. The bar plot shows that the number of in-patient hospital complication was increased in men as compared to women, while mortality, on the other hand, was higher in women.

Diabetes mellitus as a secondary diagnosis was also associated with higher mortality following a stroke; a statistically notable sex difference, however, was not seen (OR 1.08; 95% Cl 1.06–1.11 in women vs. OR 1.11; 95% Cl 1.08–1.13 in men; $p = 0.168$). Higher mortality was also associated with a previous stroke (OR 1.27; 95% Cl 1.23–1.31 in women vs. OR 1.32; 95% Cl 1.28–1.36 in men; $p = 0.112$), chronic limb threatening ischemia (OR 1.74; 95% Cl 1.61–1.88 in women vs. OR 1.77; 95% Cl 1.64–1.90 in men; $p = 0.775$). Statistically notable differences between women and men were also not found in the aforementioned co-morbidities.

The results in this dataset further revealed that hypertension as a secondary diagnosis was associated with a lower mortality rate in both women and men, showing an even lower risk for women as compared to men (OR 0.49; 95% Cl 0.48–0.50 in women vs. OR 0.57; 95% Cl 0.55–0.58 in men). This was equally true for dyslipidemia (OR 0.33; 95% Cl 0.32–0.34 vs.

OR 0.39; 95% Cl 0.38–0.40) and dementia (OR 0.74; 95% Cl 0.72–0.77 vs. OR 0.91; 95% Cl 0.88–0.95).

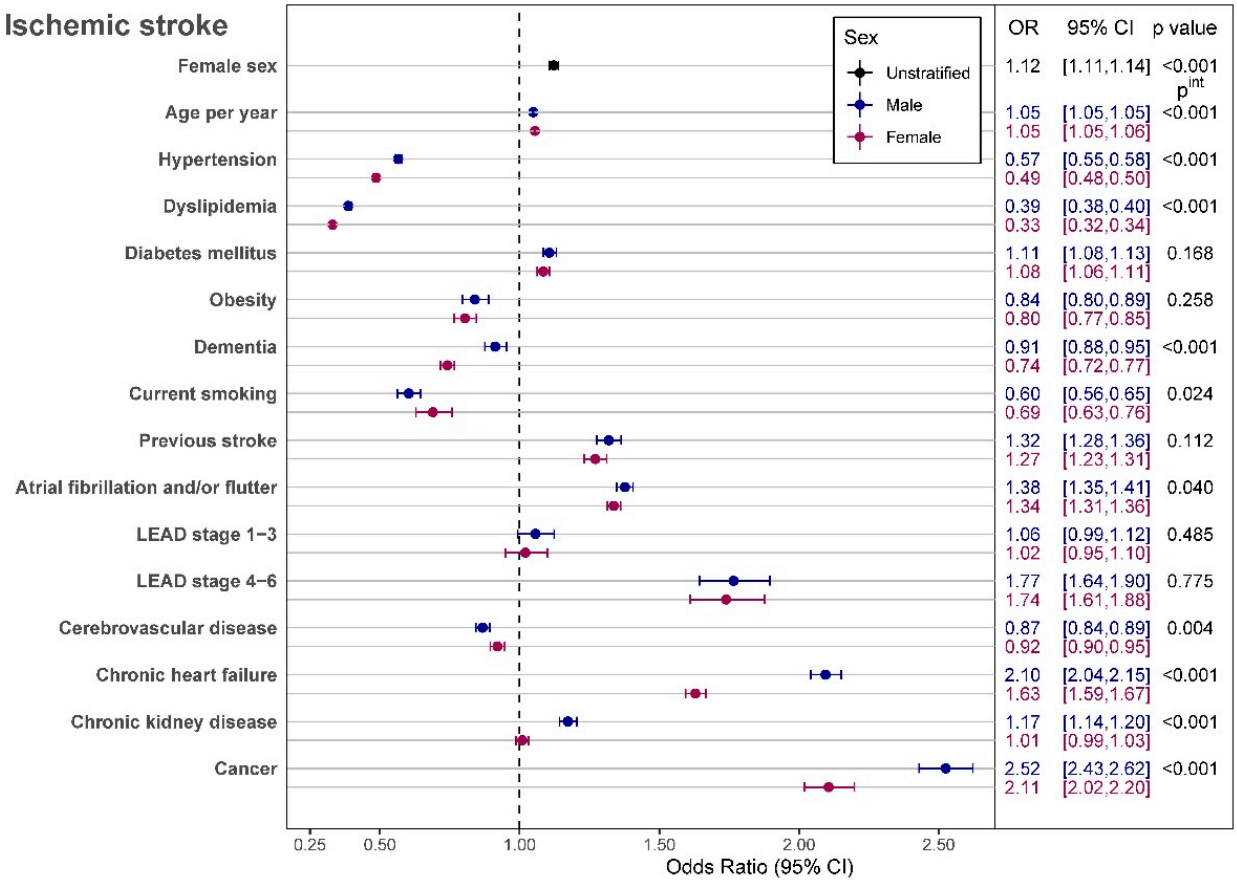

Figure 2. Forest plot of a multivariable logistic regression analysis for ischemic cerebral infarction from 2014 to 2019, evaluating the association of sex and in-hospital death. Data were adjusted by patients' age and risk profile. The analysis included the following secondary diagnoses: hypertension, dyslipidemia, diabetes mellitus, obesity, dementia, current smoking, previous stroke, atrial fibrillation and/or flutter, lower extremity artery disease, cerebrovascular disease, chronic heart failure, chronic kidney disease, cancer. LEAD denotes lower extremity artery disease.

4. Discussion

In the current study, a nationwide dataset of ischemic cerebral infarction cases covering the years between 2014 and 2019 was investigated. The data at hand revealed significant differences in the baseline characteristics of ischemic stroke patients between men and women: women had an overall higher incidence of arterial hypertension, arterial fibrillation, chronic heart failure, chronic kidney disease and dementia, but were, on the other hand, less affected than men with respect to cerebrovascular and coronary heart disease, diabetes mellitus, dyslipidemia, and previous CABG.

Co-morbidities are an important indicator of stroke prevalence and hospital outcome and overlap in general between men and women [11]. A multivariable statistical analysis for in-hospital mortality revealed, however, that the impact of most of the aforementioned co-morbidities was less severe for women as compared to men. This was notably also the case for arterial fibrillation, which occurred more frequently in women in our dataset, but has in contrast been shown in previous studies to be associated with more severe strokes in women [6,12–14]. The preventive effect of hypertension and dyslipidemia revealed by our data analysis might be explained by the fact that these patients had been treated with medication and are therefore in a healthier condition and have a better prognosis after stroke [15].

The finding as to why women in our study were, in general, less affected by crucial co-morbidities but still died earlier is an important point of discussion. One could speculate that, due to physiological differences, women suffer more severe strokes, so they die before further life-threatening complications occur. However, our data unfortunately do not allow any conclusions to be drawn in that regard.

In our dataset, women suffering from an acute ischemic cerebral infarction were, according to the median, older (79 vs. 73), and in-hospital mortality in women was higher compared to men. Since age is a risk factor for an increased incidence and severity in strokes, a longer life expectancy could explain the higher stroke mortality rate in women. However, a multivariable logistic regression analysis including age revealed that in-hospital mortality was still significantly increased in women. This finding confirms the results of previous research on post-stroke mortality, showing in general a poorer outcome for women [1,2,16–19].

4.1. Impact of In-Hospital Treatment

Routine clinical treatments for patients in our dataset with acute ischemic stroke were performed less frequently in women than in men. These include carotid EA, carotid stent, hematoma drainage, renal replacement therapy and administration of GpIIb/IIIa inhibitors. These treatments were performed roughly twice as often in men than in women. Again, our data confirm the findings of previous research on post-stroke therapeutic interventions, indicating that women are less likely to receive the same amount of treatments as compared to age-adjusted men [1–3,17,20]. This has also been shown for other routine stroke examinations such as angiographies, echocardiograms, brain imaging, Doppler examination, revascularization therapies and thrombolytic treatment [2–5,21]. Sex-specific differences in stroke interventions in our dataset could also be explained by the fact that women were older than men. However, in a recent study by Kuehnemund et al. investigating sex differences in acute myocardial infarction, it was reported that differences in the number of treatments between men and women increased with age, indicating that women received fewer diagnostic catheterizations, PCI or CABG than men at the same age [10]. It could be argued here that older women might appear frailer than men and, thus, be less likely to undergo invasive interventions. However, this possible association would need to be confirmed by further systematic studies. This also holds true for reports showing women have a longer door-to-needle and door-to-image time [1,6,21], which would have a major impact considering how time-critical stroke treatment is. As a possible explanation, researchers point out that women often have more nonspecific symptoms, such as disorientation, generalized weakness or changes in consciousness [2,3,16,22]. The life situation of older women therefore also needs to be taken into consideration. When people live alone, immediate hospitalization is less likely.

4.2. Strengths and Limitations

One of the strengths of our analysis is the large number of unselected cases, comprising all nationwide hospitalizations for acute ischemic stroke in Germany. Since ICD and OPS codes directly affect hospital reimbursement, the validity and reliability of the data are very high. In addition, due to the impact of hospital reimbursement, all diagnostic and procedural codes are independently verified by the MDK (Medizinischer Dienst der Krankenversicherung/Medical Service of the Health Insurance).

However, this study also has several limitations. The data were case-based, not patient-based, which could result in some patients being counted twice within the study period.

Furthermore, the database reflects only the hospital stay and no follow-up information after discharge and post-hospitalization care. Additionally, the data did not contain all clinically important information that might have influenced the outcome, e.g., data about localization and extent of stroke. Moreover, there was no information in the dataset about onset of symptoms or door-to-needle time, as these factors have a major impact on treatment success.

5. Conclusions

In total, the analysis of the current dataset showed that co-morbidities had a smaller impact on the mortality risk after stroke in women than in men. In addition, women were less likely to have clinical complications than men. Yet, our age-adjusted multiple regression analysis revealed a higher mortality rate after stroke in women. This might be associated with our observation that women received fewer treatments. The lower treatment rate in women is indeed in line with results of previous studies. Physical frailty in elderly women might be a factor to explain this phenomenon. However, it has also been speculated that fewer and delayed treatments could partly be attributed to the fact that women show different, more diffuse symptoms after stroke with atypical signs. Undetected symptoms could delay both hospitalization and a fast and appropriate stroke intervention. However, further studies are needed to confirm these assumptions, and to investigate the relevant physiological and epidemiological sex-specific differences, to better understand the higher mortality rate in women after stroke.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ctn6030023/s1, Supplementary Table S1: ICD-10-GM and OPS codes (Diagnosis and Procedures). Supplementary Table S2: ICD-10-GM and OPS codes (Definitions of complications and procedures). Supplementary Table S3: Results of logistic regression without interaction. Supplementary Table S4: Results of logistic regression with interaction between sex and all covariables.

Author Contributions: H.R., J.K.: study design; J.F., J.K.: Data retrieval, routine data structure, advisory support in project planning; J.F., J.K.: statistical analysis; C.L., J.K.: drafting of the initial manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: The project upon which this publication is based was funded by The Federal Joint Committee, Innovation Committee (G-BA, Innovationsfonds, number 01VSF18051). The study was conducted within the framework of the GenderVasc project (Gender-specific real care situation of patients with arteriosclerotic cardiovascular diseases).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Landesaerztekammer Westfalen-Lippe and the Medical Faculty of the University Muenster (No 2019-21-f-S).

Informed Consent Statement: As for anonymity of the data, no prior written informed consent for the analyzed data had to be obtained.

Data Availability Statement: The authors confirm that the data utilized in this study cannot be made available in the manuscript, the supplemental files, or in a public repository due to German data protection laws ('Bundesdatenschutzgesetz', BDSG). Generally, access to data of statutory health insurance funds for research purposes is possible only under the conditions defined in German Social Law (SGB V § 287). Requests for data access can be sent as a formal proposal specifying the recipient and purpose of the data transfer to the appropriate data protection agency. Access to the data used in this study can only be provided to external parties under the conditions of the cooperation contract of this research project and after written approval by the sickness fund.

Acknowledgments: We thank Christiane Engelbertz for her support in creating the revised version and with formatting.

Conflicts of Interest: H.R. reports personal fees from Daiichi, Pfizer, MedUpdate, StreamedUp, DiaPlan, NeoVasc, Pluristem, NovoNordisk and Corvia. Furthermore, institutional grants were received from Pluristem, BMS, Pfizer, Bard and Biotronik. All other authors declare no conflict of interest.

Abbreviations

AKI	Acute kidney injury
BMS	Bare-metal stent
CABG	Coronary artery bypass grafting
CI	Confidence interval
DES	Drug-eluting stent
DESTATIS	Statistisches Bundesamt (Federal Statistical Office)
EA	Endarterectomy
GP IIb/IIIa inhibitors	Glycoprotein IIb/IIIa inhibitors
ICD	International Statistical Classification of Diseases and Related Health Problems
ICH	Intracerebral hemorrhage
LEAD	Lower extremity arterial disease
LV- CHF	Left ventricular chronic heart failure
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
OPS	German Procedure Classification
OR	Odds ratio
RF	Rutherford
RV- CHF	Right ventricular chronic heart failure
Yr	year

References

1. Persky, R.W.; Turtzo, L.C.; McCullough, L.D. Stroke in Women: Disparities and Outcomes. *Curr. Cardiol. Rep.* **2010**, *12*, 6–13. [CrossRef] [PubMed]
2. Girijala, R.L.; Sohrabji, F.; Bush, R.L. Sex differences in stroke: Review of current knowledge and evidence. *Vasc. Med.* **2017**, *22*, 135–145. [CrossRef] [PubMed]
3. Asdaghi, N.; Romano, J.G.; Wang, K.; Ciliberti-Vargas, M.A.; Koch, S.; Gardener, H.; Dong, C.; Rose, D.Z.; Waddy, S.P.; Robichaux, M.; et al. Sex disparities in Ischemic Stroke Care FL-PR CReSD (Florida-Puerto Rico Collaboration to reduce Stroke disparities). *Stroke* **2016**, *47*, 2618–2626. [CrossRef] [PubMed]
4. Reid, J.M.; Dai, D.; Gubitz, G.J.; Kapral, M.K.; Christian, C.; Phillips, S.J. Gender Differences in Stroke Examined in a 10-Year Cohort of Patients Admitted to a Canadian Teaching Hospital. *Stroke* **2008**, *39*, 1090–1095. [CrossRef]
5. Towfighi, A.; Markovic, D.; Ovbiagele, B. Sex Differences in Revascularization Interventions after Acute Ischemic Stroke. *J. Stroke Cerebrovasc. Dis.* **2013**, *22*, e347–e353. [CrossRef] [PubMed]
6. Corbière, S.; Tettenborn, B. Stroke in women: Is it different? *Clin. Transl. Neurosci.* **2021**, *5*, 1–8. [CrossRef]
7. Berglund, A.; Schenck-Gustafsson, K.; von Euler, M. Sex differences in the presentation of stroke. *Maturitas* **2017**, *99*, 47–50. [CrossRef]
8. Spaander, F.H.; Zinkstok, S.M.; Baharoglu, I.M.; Gensicke, H.; Polymeris, A.; Traenka, C.; Hametner, C.; Ringleb, P.; Curtze, S.; Martinez-Majander, N.; et al. Thrombolysis in Ischemic Stroke Patients Collaborators (TrISP). Sex Differences and Functional Outcome After Intravenous Thrombolysis. *Stroke* **2017**, *48*, 699–703, Erratum in *Stroke* **2017**, *48*, e97. [CrossRef]
9. Cadilhac, D.A.; Kim, J.; Lannin, N.A.; Kapral, M.K.; Schwamm, L.H.; Dennis, M.S.; Norrving, B.; Meretoja, A. National stroke registries for monitoring and improving the quality of hospital care: A systematic review. *Int. J. Stroke* **2015**, *11*, 28–40. [CrossRef]
10. Kuehnemund, L.; Koeppe, J.; Feld, J.; Wiederhold, A.; Illner, J.; Makowski, L.; Gerß, J.; Reinecke, H.; Freisinger, E. Gender differences in acute myocardial infarction—A nationwide German real-life analysis from 2014 to 2017. *Clin. Cardiol.* **2021**, *44*, 890–898. [CrossRef]
11. Peters, S.A.; Carcel, C.; Millett, E.R.; Woodward, M. Sex differences in the association between major risk factors and the risk of stroke in the UK Biobank cohort study. *Neurology* **2020**, *95*, e2715–e2726. [CrossRef] [PubMed]
12. Emdin, C.A.; Wong, C.; Hsiao, A.J.; Altman, D.G.; Peters, S.; Woodward, M.; Odutayo, A.A. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: Systematic review and meta-analysis of cohort studies. *BMJ* **2016**, *352*, h7013. [CrossRef] [PubMed]
13. Lang, C.; Seyfang, L.; Ferrari, J.; Gattringer, T.; Greisenegger, S.; Willeit, K.; Toell, T.; Krebs, S.; Brainin, M.; Kiechl, S.; et al. Do Women With Atrial Fibrillation Experience More Severe Strokes? Results From the Austrian Stroke Unit Registry. *Stroke* **2017**, *48*, 778–780. [CrossRef]
14. Christensen, H.; Bushnell, C. Stroke in Women. *Contin. Lifelong Learn. Neurol.* **2020**, *26*, 363–385. [CrossRef] [PubMed]
15. Hoffmann, F.; Fassbender, P.; Zander, W.; Ulbrich, L.; Kuhr, K.; Adler, C.; Halbach, M.; Reuter, H. The Hypertension Paradox: Survival Benefit After ST-Elevation Myocardial Infarction in Patients with History of Hypertension. A Prospective Cohort- and Risk-Analysis. *Front. Cardiovasc. Med.* **2022**, *9*, 785657. [CrossRef]

16. Ali, M.; van Os, H.J.; van der Weerd, N.; Schoones, J.W.; Heymans, M.W.; Kruyt, N.D.; Visser, M.C.; Wermer, M.J. Sex Differences in Presentation of Stroke: A Systematic Review and Meta-Analysis. *Stroke* **2022**, *53*, 345–354. [CrossRef] [PubMed]
17. Lisabeth, L.D.; Reeves, M.J.; Baek, J.; Skolarus, L.E.; Brown, D.; Zahuranec, D.B.; Smith, M.A.; Morgenstern, L.B. Factors Influencing Sex Differences in Poststroke Functional Outcome. *Stroke* **2015**, *46*, 860–863. [CrossRef]
18. Gall, S.L.; Donnan, G.; Dewey, H.M.; Macdonell, R.; Sturm, J.; Gilligan, A.; Srikanth, V.; Thrift, A.G. Sex differences in presentation, severity, and management of stroke in a population-based study. *Neurology* **2010**, *74*, 975–981. [CrossRef]
19. Gall, S.; Phan, H.; Madsen, T.E.; Reeves, M.; Rist, P.; Jimenez, M.; Lichtman, J.; Dong, L.; Lisabeth, L.D. Focused Update of Sex Differences in Patient Reported Outcome Measures After Stroke. *Stroke* **2018**, *49*, 531–535. [CrossRef]
20. Strong, B.; Lisabeth, L.D.; Reeves, M. Sex differences in IV thrombolysis treatment for acute ischemic stroke. *Neurology* **2020**, *95*, e11–e22. [CrossRef]
21. Oluwole, S.A.; Wang, K.; Dong, C.; Ciliberti-Vargas, M.A.; Gutierrez, C.M.; Yi, L.; Romano, J.G.; Perez, E.; Tyson, B.A.; Ayodele, M.; et al. Disparities and Trends in Door-to-Needle Time: The FL-PR CReSD Study (Florida-Puerto Rico Collaboration to Reduce Stroke Disparities). *Stroke* **2017**, *48*, 2192–2197. [CrossRef] [PubMed]
22. Colsch, R.; Lindseth, G. Unique Stroke Symptoms in Women: A Review. *J. Neurosci. Nurs.* **2018**, *50*, 336–342. [CrossRef] [PubMed]