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Zaburzenia emocjonalne po udarze mózgu: ocena częstości występowania, wpływ majaczenia. Związek depresji poudarowej z poziomem białka C- reaktywnego i jej wpływ na rokowanie.

Post-stroke emotional disturbances: prevalence, impact of delirium. Relationship of post-stroke depression with C-reactive protein level and its influence on prognosis.

Praca doktorska

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Pracę wykonano w Katedrze i Klinice Neurologii UJ CM w Krakowie
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Kraków, rok 2020

Spis treści

I. Wykaz publikacji stanowiących rozprawę doktorską

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   Tytuł: Delirium Post-Stroke: Short- and Long-Term Effect on Depression, Anxiety, Apathy and Aggression (Research Study—Part of PROPOLIS Study).
   Czasopismo: Journal of Clinical Medicine (2020) 9(7):2232

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   Tytuł: Early Depression Independently of Other Neuropsychiatric Conditions, Influences Disability and Mortality after Stroke (Research Study-Part of PROPOLIS Study).
   Czasopismo: Biomedicines (2020) 8(11):509

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   Tytuł: C-reactive protein and post-stroke depressive symptoms.
   Czasopismo: Scientific Reports (2020) 10(1):1431

II. Wstęp

Zaburzenia emocjonalne są częstym następstwem udaru mózgu. Mogą pojawić się już w ostrej fazie choroby lub w ciągu kolejnych miesięcy. Biorąc pod uwagę zróżnicowany czas dokonywania pomiaru, szacuje się, że depresja poudarowa (PSD) występuje u około 20-50% pacjentów [1,2], lęk poudarowy (PSA) u 20-25% [3], zachowania agresywne pojawiają się u około 30% [4,5], a apatia u od 15% do nawet 70% pacjentów [6].

Depresja poudarowa związana jest z gorszą jakością życia, większą niepełnosprawnością i śmiertelnością [2,7]. Istotnie też koreluje z obniżeniem sprawności poznawczej, zwłaszcza w obszarze pamięci i uwagi [8,9,10]. Rosnąca liczba badań pokazuje, że wystąpienie objawów depresyjnych jest związane z mechanizmami immunologicznymi, m.in. podwyższonym stężeniem białka C-reaktywnego (CRP) [11,12,13]. CRP jest biomarkerem zapalnym, którego poziom wzrasta w ostrej fazie stanu zapalnego. Pacjenci z depresją poudarową charakteryzują się zwiększonym stężeniem CRP w krwi obwodowej [14,15], a wyniki badań wskazują, że podwyższony poziom CRP wraz z innymi markerami zapalenia pozwala przewidywać rozwój depresji [16] oraz oporność na farmakoterapię przeciwdepresyjną [17].

Dane dotyczące PSA są niejednoznaczne. Część badaczy sugeruje, że PSA wiąże się z osłabioną sprawnością w wykonywaniu codziennych czynności zarówno bezpośrednio, jak i do 3 lat po udarze [18]. Z kolei inni, nie wykazali takiego związku [19,20].

Zachowania agresywne po udarze mogą znacząco zakłócać przebieg leczenia i rehabilitacji oraz być czynnikiem stresogennym dla członków rodziny, personelu medycznego i samego pacjenta [21]. Wyniki badań

pokazują też, że agresja poudarowa częściej współwystępuje z PSD i PSA [7].

Apatia po udarze mózgu wiąże się z większą zależnością w codziennym funkcjonowaniu, a także z wydłużonym czasem hospitalizacji i mniejszym zaangażowaniem w rehabilitację [22, 23].

Poza pojawieniem się zaburzeń emocjonalnych, częstym następstwem udaru mózgu jest wystąpienie delirium, które według szacunków dotyka między 10.2 a 48% hospitalizowanych pacjentów [24,25]. Wystąpienie delirium poudarowego wiąże się z wydłużonym czasem hospitalizacji, zwiększoną śmiertelnością i zaburzeniami poznawczymi [26,27,28]. Ponadto wcześniejsze badania wiązały wystąpienie delirium ze zwiększonym ryzykiem długotrwałych problemów w obszarze zdrowia psychicznego, jednakże rezultaty nie są jednoznaczne.[tutaj jakies piśmiennictwo}

Tematem niniejszej pracy są zagadnienia dotyczące zaburzeń emocjonalnych po udarze mózgu. Przedstawione zostaną wyniki badań nad rozpowszechnienieniem depresji, lęku, apatii i agresji u hospitalizowanych pacjentów, u których wystąpiło lub nie delirium w ostrej fazie udaru. Zostanie pokazana rola depresji poudarowej, jako istotnego czynnika zwiększającego ryzyko niepełnosprawności oraz śmiertelności 3 i 12 miesięcy po udarze. Zostanie również przedstawiony związek pomiędzy wystąpieniem depresji w ostrej fazie udaru oraz 3 miesiące po nim, a stężeniem białka C-reaktywnego u hospitalizowanych pacjentów.

III. Cele pracy

Celem pracy będzie:

1. Określenie częstości występowania zaburzeń emocjonalnych (depresji, lęku, apatii, agresji) u pacjentów po udarze mózgu, a także sprawdzenie związku pomiędzy wystąpieniem delirium w ostrej fazie udaru a depresją, lękiem apatią i agresją poudarową.

2. Ocena wpływu depresji poudarowej na zmiany w funkcjonowaniu (ocena poziomu niepełnosprawności) i śmiertelność po 3 i 12 miesiącach od udaru.

3. Zbadanie związku między stężeniem białka c-reaktywnego we krwi a wystąpieniem objawów depresyjnych po udarze niedokrwiennym u hospitalizowanych pacjentów i 3 miesiące po udarze.

IV. Teksty opublikowanych prac naukowych będących podstawą pracy doktorskiej

Journal of
Clinical Medicine

MDPI

Article

Delirium Post-Stroke: Short- and Long-Term Effect on Depression, Anxiety, Apathy and Aggression (Research Study—Part of PROPOLIS Study)

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Received: 1 June 2020; Accepted: 13 July 2020; Published: 14 July 2020

Abstract: Background: Stroke patients are particularly vulnerable to delirium episodes, but very little is known about its subsequent adverse mental health outcomes. The author's objective was to explore the association between in-hospital delirium and depression, anxiety, anger and apathy after stroke. Methods: A total of 750 consecutive patients with acute stroke or transient ischemic attack, were screened for delirium during hospitalization. Patients underwent mental health evaluation in hospital, 3 and 12 months post-stroke; depression, apathy, anxiety and anger were the outcomes measured at all evaluation check points. Results: Delirium was an independent risk factor for depression (OR = 2.28, 95%CI 1.15–4.51, $p = 0.017$) and aggression (OR = 3.39, 95%CI 1.48–7.73, $p = 0.004$) at the hospital, for anxiety 3 months post-stroke (OR = 2.83, 95%CI 1.25–6.39, $p = 0.012$), and for apathy at the hospital (OR = 4.82, 95%CI 2.25–10.47, $p < 0.001$), after 3 (OR = 3.84, 95%CI 1.31–11.21, $p = 0.014$) and 12 months (OR = 4.95, 95%CI 1.68–14.54, $p = 0.004$) post stroke. Conclusions: The results of this study confirm, that mental health problems are very frequent complications of stroke. Delirium in the acute phase of stroke influences mental health of patients. This effect is especially significant in the first months post-stroke and vanishes with time, which suggests that in-hospital delirium might not be a damaging occurrence in most measures of mental health problems from a long-term perspective.

Keywords: stroke; post-stroke delirium; depression; anxiety; apathy; aggression

1. Introduction

Among different neurological conditions stroke is a major risk factor for development of delirium [1]. Its prevalence in the in-hospital population ranges from 10.2 [2] to 48% [1]. The evidence suggests that, although the overt symptoms of delirium may be short lived, there may be a lasting impact of delirium on the long-term prognosis. There has been an increasing interest in the effect of delirium on healthcare outcomes. Previous research has linked post-stroke delirium with increased length of hospital stay [3], dependence, mortality [4], and cognitive impairment [5].

It has been shown that a substantial number of stroke survivors develop long term mental health problems such as anxiety, anger, depression, fear and others that have a negative influence on recovery, limit social reintegration of the persons with stroke, reduce quality of life, and are a source of caregiver

burnout [6]. Moreover, previous research has associated delirium with an increased risk of long term mental health problems in different in-hospital populations; however, the data are equivocal [7]. Little is known about the effects of in-hospital delirium on mental health outcomes among stroke survivors.

One can hypothesize that delirium in acute phase of stroke can impact the mental health problems like depression, anxiety, apathy and anger. Therefore, the author's objective in this prospective study was to investigate the influence of in-hospital delirium on patients' psychiatric conditions in short- and long-term time perspective following stroke.

2. Materials and Methods

This study was conducted as part of a larger study, known as the PROPOLIS study, which investigated prevalence, risk factors, short- and long-term prognosis among patients with post-stroke delirium. Testing took place in the stroke unit at the University Hospital and Outpatients Clinique at the Neurology Department, University Hospital, Krakow. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. Informed written consent was provided by each participant or a caregiver. The Local Bioethics Committee of Jagiellonian University approved the study (KBET/63/B/2014).

2.1. Population and Design

The 750 consecutive patients with stroke (ischemic/hemorrhagic) or transient ischemic attack admitted to the stroke unit at the University Hospital in Krakow meeting the inclusion criteria for this study (Patients > 18 years of age, admitted within 48 h from the first stroke symptoms, speaking Polish) were investigated for the presence and risk factors of delirium. Patients were screened for delirium every day from admission to the 7th day of hospitalization with the abbreviated version of Confusion Assessment Method (bCAM) or the Intensive Care Units version (CAM-ICU), specifically in patients with motor aphasia or those who could not communicate for other reasons [8,9]. Delirium symptoms' severity was assessed using the Cognitive Test for Delirium [10].

A resident neurologist trained in delirium diagnosis was responsible for screening for delirium, and a trained psychologist was responsible for cognitive, behavior/emotional assessment. The senior neurologist/neuropsychologist was responsible for evaluating all data. The physicians rating the patients in the hospital did not change during the study.

Due to the abrupt and fluctuating course of delirium, a short questionnaire regarding each patients' behavior and cognitive status was completed by ward nurses throughout the entire hospitalization, 24 h per day, then analyzed by raters, in order not to miss any possible fluctuations of attention and awareness.

The final diagnosis of delirium was based on both clinical observation and structural assessment. The diagnostic criteria for delirium were based on the DSM-5 classification [11]. For those patients who were not able to undergo formal cognitive evaluation, the diagnosis was based on clinical observation and DSM-5 criteria for delirium. The raters were responsible for consensus of the diagnosis, if there were doubts then, the final diagnosis relied upon the senior neurologist.

Data were collected regarding socio-demographic factors and clinical features of patients. The details of the procedures were described elsewhere [4]. The Cumulative Illness Rating Scale (CIRS) was used as a general indicator of health status [12]. On admission information were obtained from the spouse/caregiver regarding pre-stroke mental and behavioral functioning on Neuropsychiatric Inventory [13]. In order to diagnose patients with pre-stroke dementia, a Polish version of Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) was used [14].

For cognitive assessment, the Montreal Cognitive Assessment (MoCA) [15] and Frontal Assessment Battery [16] were performed between day 1–2 and on the 7th day after admission.

All patients had neuroimaging (CT/MRI) performed on admission. Furthermore, upon admission, patients were screened for the severity of clinical deficit, which was graded by the National Institutes

of Health Stroke Scale (NIHSS) [17]. Disabilities prior to admission were assessed by the modified Rankin Scale (mRS) [18].

The primary endpoint of this study was the influence of in-hospital delirium on mental health problems after 3 and 12 months post-stroke. The secondary end point was to assess the prevalence of depression, apathy, anxiety and anger after 3 and 12 months post-stroke.

2.2. Outcome Assessment

We assessed the following outcome measures: presence of depression, apathy, anxiety and anger (aggression/ hostility) between 7–10 days after admission to the hospital and during a follow-up visit 3 and 12 months after the stroke. Patients who did not attend a follow-up visit were contacted by phone and the information was gathered. A neurologist and a psychologist, both uninvolved in the baseline assessment of patients, were responsible for data acquisition.

2.3. Outcome Methods

The presence of depressive symptoms was assessed by Patient Health Questionnaire (PHQ-9) [19]. These items are used to query symptoms present over the last 2 weeks using 4-point Likert scale with item scores ranging from 0 (symptoms not present) to 3 (symptoms present nearly every day). The score ranges from 0 (no depressive symptoms) to 27 (all symptoms occurring nearly every day) and can be used to determine depression severity (0–4 indicates no depression, 5–9 mild depression, 10 to 14 moderate depression, 15–19 moderately severe depression and 20–27 severe depression). This method shows good reliability, validity and clinical utility when used in stroke patients [20].

To evaluate post-stroke apathy (PSA) the Apathy Evaluation Scale-C (AES-C) [21] was used. AES is an 18-item questionnaire with a clinician rated version that was applied in this study. The questions address patient's activities, interest in doing things, relationship with others and feelings over the past two to three weeks. Each item is rated on a 4-point Likert scale with item scoring ranging from 1 (not at all true) to 4 (very true). The total AES-C score range from 18 to 72, with higher scores indicating greater apathy. The AES has good reliability and validity and was frequently used in studies on post-stroke apathy [21]. Apathy was diagnosed with AES score of ≥37 points [22].

Anxiety was measured with Polish adaptation of State Trait Anxiety Inventory (STAI) [23,24], the 40-item instrument, measuring respectively transient and enduring levels of anxiety. The state scale used in the present study administered as a self-completion questionnaire by the interviewer, assessed how the patients felt at the moment or in the recent past and how they anticipate their feelings to be in a specific, hypothetic situation in the future. STAI scale is scored on four levels of anxiety intensity from 1 (not at all) to 4 (very much) and with a sum score between 20 and 80. The raw results are interpreted by referring to a relevant sten scores and then categorized into three levels of anxiety: low (1–4 sten), moderate (5–6 sten) and high (7–10 sten) [24].

To assess anger, a Polish version of the Buss–Durkee Hostility Inventory (BDHI) was applied [25,26]. The BDHI is a 75-item questionnaire developed to assess Assault—physical violence against others; Indirect hostility—both roundabout and undirected aggression; Irritability—readiness to explode with negative affect at the slightest provocation; Negativism—oppositional behavior, usually against authority; Resentment—jealousy and hatred of others; Suspicion—projection of hostility onto others; Verbal hostility—negative affect expressed in both the style and content of speech; Guilt—feelings of being bad, having done wrong. The first seven sub-classes can be grouped into two factors. Resentment and Suspicion make up the factor Hostility, while Assault, Indirect hostility, Irritability and Verbal hostility sub-classes form the factor Aggression. The first factor, Hostility, reflects the cognitive components of anger while the Aggression factor reflects the behavioral components [26].

2.4. Statistics

Statistical analysis was performed using Statistica 13.3 software (StatSoft®, Kraków, Poland). Quantitative variables were presented as arithmetic means with standard deviations (SDs), or medians

with interquartile ranges (IQRs), and depending on normal or non-normal distribution, were compared with the Student's t-test or Mann–Whitney U test, respectively. Qualitative variables were compared using the chi-squared test with or without Yates' correction. Considerable demographic and clinical factors were analyzed in univariate logistic regression models, and predictive values of delirium, presented as odds ratios (ORs) with 95% confidence intervals (CIs), on post-stroke depression, apathy, anxiety and aggression/hostility assessed in hospital and at follow-up visits were calculated. Then, delirium and other variables at p-value < 0.1 in the univariate analyses were included as potential predictors into multivariate logistic regression models in search of delirium as an independent risk factor using a forward stepwise selection method. p-values < 0.05 were considered statistically significant.

3. Results

Of the 750 patients included to this study, 682 were dismissed from the hospital and scheduled for the follow-up visits. A flowchart shows the study design (Figure 1).

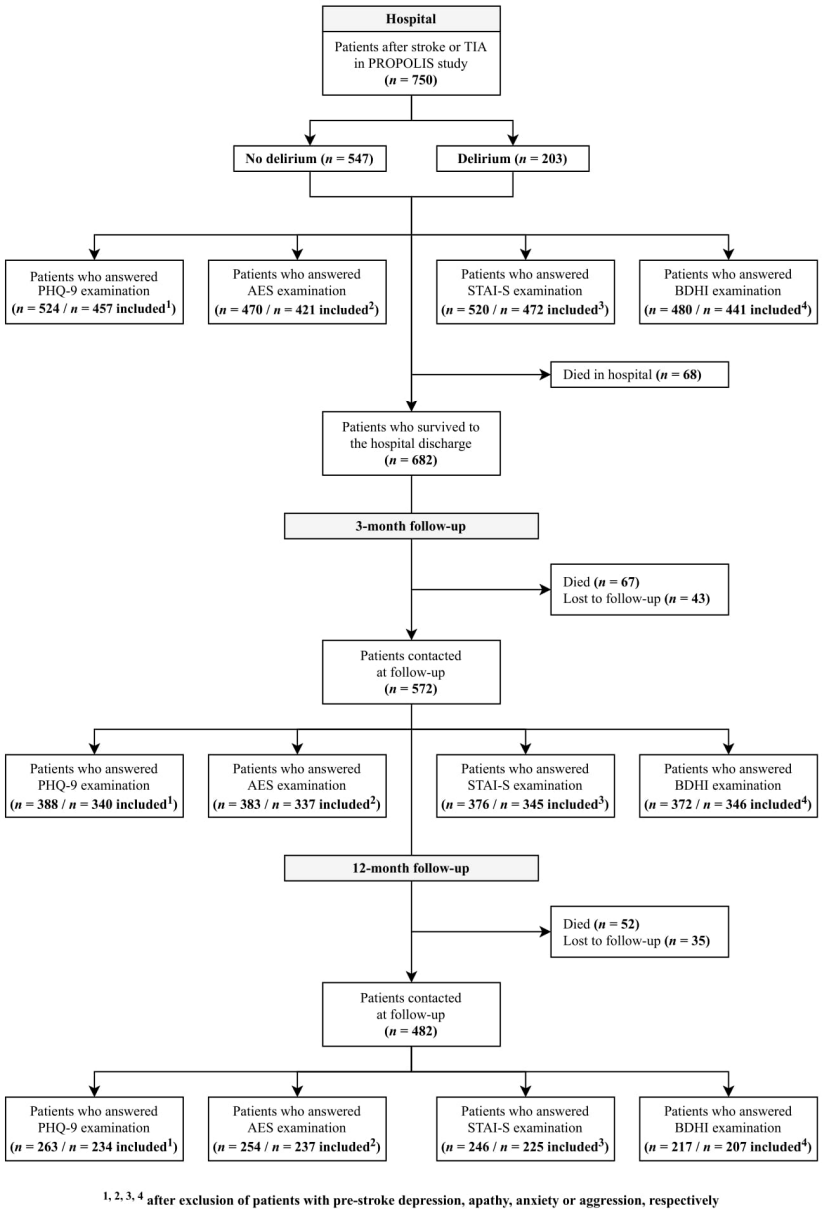

Figure 1. Study flowchart.

The prevalence of depression, apathy, fear and aggression/hostility at the hospital, 3 and 12 months post-stroke among patients with and without mental health problems prior to admission, among patients with and without delirium at the hospital is shown in Table 1 (the comparison of mental health problems' prevalence between patients with and without delirium is shown in Table S1).

Table 1. The prevalence of depression, apathy, fear and aggression/hostility among patients with and without mental health problems prior to admission.

Time of Examination	Mental Health Problem	All Patients, *n* (%)	Patients without Delirium, *n* (%)	Patients with Delirium, *n* (%)
	Depression PHQ-9 score ≥ 5			
Hospital		286/524 (54.58)	220/433 (58.81)	66/91 (72.53)
Hospital *		234/457 (51.20)	181/384 (47.14)	53/73 (72.60)
3 months		227/388 (58.51)	181/329 (55.02)	46/59 (77.97)
3 months *		191/340 (56.18)	157/294 (53.40)	34/46 (73.91)
12 months		144/263 (54.75)	127/234 (54.27)	17/29 (58.62)
12 months *		122/234 (52.14)	111/212 (52.36)	11/22 (50.00)
	Apathy AES-C score ≥ 37			
Hospital		169/470 (35.96)	116/395 (39.27)	53/75 (70.67)
Hospital *		132/421 (31.35)	92/360 (25.56)	40/61 (65.57)
3 months		150/383 (39.16)	107/324 (33.02)	43/59 (72.88)
3 months *		117/337 (34.72)	89/294 (30.27)	28/43 (65.12)
12 months		70/254 (27.56)	53/226 (23.45)	17/28 (60.71)
12 months *		57/231 (24.68)	44/209 (21.05)	13/22 (59.09)
	Anxiety STAI sten score ≥ 7			
Hospital		164/520 (31.54)	126/429 (29.37)	38/91 (41.76)
Hospital *		137/472 (29.03)	103/388 (26.55)	34/84 (40.48)
3 months		103/376 (27.39)	76/321 (23.68)	27/55 (49.09)
3 months *		93/345 (26.96)	68/294 (23.13)	35/51 (49.02)
12 months		48/246 (19.51)	41/219 (18.72)	7/27 (25.93)
12 months *		38/225 (16.89)	31/199 (15.58)	7/26 (26.92)
	Aggression/hostility BDHI score			
Hospital	'Aggression' sten score ≥ 7	45/480 (9.38)	32/401 (7.98)	13/79 (16.46)
	'Hostility' sten score ≥ 7	238/480 (49.58)	178/401 (44.39)	60/79 (75.95)
Hospital *		38/441 (8.62)	27/368 (7.34)	11/73 (15.07)
		213/441 (48.30)	158/368 (42.93)	55/73 (75.34)
3 months	'Aggression' sten score ≥ 7	37/372 (9.95)	31/318 (9.75%)	6/54 (11.11)
	'Hostility' sten score ≥ 7	79/372 (21.24)	63/318 (19.81)	16/54 (29.63)
3 months *		35/346 (10.12)	29/297 (9.76)	6/49 (12.24)
		74/346 (21.39)	58/297 (19.53)	16/49 (32.65)
12 months	'Aggression' sten score ≥ 7	16/217 (7.37)	14/197 (7.11)	2/20 (10.00)
	'Hostility' sten score ≥ 7	48/317 (22.12)	44/197 (22.34)	4/20 (20.00)
12 months *		15/207 (7.25)	13/187 (6.95)	2/20 (10.00)
		44/207 (21.26)	40/187 (21.39)	4/20 (20.00)

* number of patients with mental health problems after exclusion patients diagnosed with particular disorder prior to stroke; PHQ-9—Patient Health Questionnaire-9; AES—Apathy Evaluation Scale; STAI-S—State-Trait Anxiety Inventory, state scale; BDHI—Buss–Durkee Hostility Inventory; 'Aggression'—assault, indirect hostility, irritability and verbal hostility; 'Hostility'—resentment and suspicion

Patients with mental health problems prior to stroke were excluded from final analyses. The diagnosis of depression, anxiety, apathy and aggression was based on NPI on admission, the CIRS psychiatric/behavioral subscale, prior medical history, and medication actually taken by the patient.

In univariate analyses, delirium was a risk factor for depression, anxiety and hostility at the hospital and after 3 months, for aggression during hospitalization and for apathy during all of the observation period (see Supplementary Materials: Tables S2–S5). In multivariable logistic regression analysis, delirium was an independent risk factor for depression and aggression during hospitalization, anxiety after 3 months and apathy during all follow-up periods. Table 2 shows the final results.

Table 2. Influence of post-stroke delirium on mental health problems during the follow-up period in univariate and multivariate logistic regression models.

	Mental Health Problem		**Univariate Logistic Regression Model**		**Multivariate Logistic Regression Model**	
Variable	**No Delirium, *n* (%)**	**Delirium, *n* (%)**	**OR (95%CI)**	***p*-Value**	**OR (95%CI)**	***p*-Value**
Depression						
in hospital PHQ-9 score ≥ 5	181/384 (47.14)	53/73 (72.60)	2.972 (1.711–5.162)	<0.001	2.286 (1.158–4.513)	0.017
Apathy						
in hospital AES score ≥ 37	92/360 (25.56)	40/61 (65.57)	5.549 (3.110–9.899)	<0.001	4.828 (2.225–10.477)	<0.001
at 3-month follow-up AES score ≥ 37	89/294 (30.20)	28/43 (65.12)	4.300 (2.190–8.442)	<0.001	3.841 (1.315–11.216)	0.014
at 12-month follow-up AES score ≥ 37	44/209 (21.05)	13/22 (59.09)	5.417 (2.175–13.493)	<0.001	4.951 (1.685–14.547)	0.004
Anxiety						
at 3-month follow-up STAI-S sten score ≥ 7	68/294 (23.13)	35/51 (49.02)	3.196 (1.732–5.895)	<0.001	2.831 (1.254–6.391)	0.012
Aggression						
in hospital BDHI 'Aggression' sten score ≥ 7	27/368 (7.34)	11/73 (15.07)	2.241 (1.057–4.751)	0.035	3.391 (1.486–7.739)	0.004

PHQ-9—Patient Health Questionnaire-9; AES—Apathy Evaluation Scale; STAI-S—State-Trait Anxiety Inventory, state scale; BDHI—Buss–Durkee Hostility Inventory; 'Aggression'—assault, indirect hostility, irritability and verbal hostility.

The detailed results of all outcome measures during the follow-up period are available in Supplementary Data (Table S6).

Forty-three patients did not follow-up after 3 months and 35 after 12 months post-stroke. Those who were omitted after 3 months were significantly older, more physically and cognitively disabled prior to stroke. The patients that failed to follow-up 12 months after stroke were significantly older, had more severe neurological deficit on admission, and were more disabled prior to stroke. Tables S13 and S14 show the results.

4. Discussion

4.1. Brief Summary of the Findings

Despite the significant impact of in-hospital delirium on prognosis and long-term functional outcome for patients with stroke, its association with mental-health problems has not yet been clarified. Our study aimed to provide insight into the impact of delirium in acute phase of stroke on mental health in short and long time perspective while controlling for other relevant predisposing factors such as age, gender cognitive and vascular comorbidity.

4.2. Prevalence of Mental Health Problems Post-Stroke

In the meta-analysis by Hackett and Pickles [27], the pooled data showed that depression was present in 31% of stroke survivors at any time up to five-years post stroke; however, its frequency varied across studies from 5% at two to five days after stroke to 84% at 3-months after stroke. The rate of post-stroke depression was much higher in our study than average in meta-analysis. We observed this rate was very stable over the follow-up period.

The frequency of apathy following stroke is estimated between 20–25% [28]. In our study, the prevalence was higher, with a tendency to decrease its rate over 12 months post-stroke.

The prevalence of anxiety after the stroke in our study was similar to what was previously observed, both in the acute phase of stroke [29] as well as over the 12 months post-stroke. We also observed that the anxiety prevalence decreased with time.

Studies of anger after stroke are difficult to compare due to large differences. The reasons for this are the different time periods covered by each study, different methodologies, or different diagnostic criteria. A meta-analysis of 18 studies (5 in acute and 13 in post-acute time of stroke), showed that anger was diagnosed between 12 to 56% of patients [30]. We observed that behavioral and cognitive components of anger are not concurrent; aggression, behavior component, was low, less than 10%, in the acute phase of stroke and hostility, cognitive component, was high, close to 50%, among patients. We also observed its decreasing prevalence over 12 months post-stroke.

4.3. In-Hospital Delirium and Mental Health Problems

Delirium and depression, complex neuropsychiatric syndromes are common post stroke, however their relationship is vague. Still there is no clear answer to the question whether depressive symptoms arise during a delirium episode and if they resolve with delirium. The widespread disruption of neural networks in delirium may incorporate affective centers in vulnerable or predisposed subjects. Nelson et al. in the review article summarized that correlation exists between depression and delirium in patients with hip fracture, but in no other specific populations [31].

One small study, recently published, analyzed the short and long-term effect of delirium on anxiety and depression among stroke patients [32]. There was no influence of delirium on depression and anxiety 1-, 6- and 12-month post-stroke. In our study, the rate of depression was significantly higher in patients with delirium only 7–10 days after stroke and specifically when patients were analyzed regardless of dementia severity. It is unclear whether the depression symptoms measured soon after stroke truly represent new psychopathology or rather denote persistent or resolving delirium. Although studies have shown that depression is a risk factor for delirium [33–35], this relationship between delirium and depression is not clearly bidirectional and delirium seems to not increase the risk for depression in the long-term perspective.

In our study in-hospital delirium was an independent risk factor for apathy during all follow-up time. The association between apathy and delirium was not an area of interest for research so far, but these two clinical mental health problems have a common relationship. Apathy and delirium share a similar clinical picture. Delirium may manifest as lack of interest in an environment and goal-directed behavior, flat affect and withdrawal which resembles apathy [36].

Apathy and delirium share also similar anatomical correlations. Apathy is associated with disruption of medial frontal cortex—in particular the anterior corpus callosum, orbito-frontal cortex and subcortical structures including the ventral striatum, medial thalamus and ventral tegmental area, or connections between these regions. These associations are demonstrated across techniques that measure underlying neuronal metabolism, gray matter atrophy, and both structural and functional connectivity in the brain [37]. Delirium is associated with abnormalities of corpus callosum, cingulum, basal forebrain, occipital, parietal and temporal lobes, cerebellum and thalamus on diffusor tension imaging [38].

Presumably, silent structural brain lesions in critical regions for apathy and delirium cause higher brain vulnerability and as a result of stroke, clinically manifest as delirium or apathy or both.

In this study, we did not correlate the precise stroke lesion with mental health problem. However, studies show, that irrespective of the stroke lesion, patients with apathy have reduced connectivity in many regions, remote from stroke, including frontal and basal ganglia regions associated with apathy [39] as well as the reduced cerebral blood flow within the basal ganglia compared to non-apathetic patients, irrespective of stroke location [40].

Anger is a frequent complication of stroke. So far, no study reported the association between anger and delirium post-stroke. We observed such a relationship only in behavioral aspect of anger (aggression) during hospitalization. At that time, there was no relationship between cognitive component (hostility) of anger and delirium. We also did not find a positive association between delirium and aggression/hostility 3- and 12-month post-stroke. Activation studies have demonstrated that anger is associated with increased cerebral blood flow in brain regions that also show increased metabolism during delirium episode [41,42]. This could explain the association between aggression and delirium only during the early phase post-stroke.

Anxiety is a normal emotion to stress like stroke, hospitalization, fear of dying, but it may become persistent and inappropriate. Anxiety at the hospital was high in both groups, insignificantly higher in patients with delirium. After 3 months, delirium was found to be an independent risk factor for anxiety. Presumably, high emotional distress and memories of frightening psychotic experiences in delirious patients may be responsible for significantly higher rates of anxiety 3 months post-stroke when compare to patients without delirium. With time, when the memories faded, the rate of anxiety went down and its prevalence was similar in both groups.

This study confirms previous results, which show that mental health problems are a frequent post-stroke complication. This study builds upon previous research in that, for the first time, a large sample of stroke patients was assessed for the impact of in-hospital delirium on stroke patients' mental health. Delirium is very rarely considered as a risk factor of long-term post-stroke prognosis. In our study, we evaluated disorders that are highly interrelated, such as delirium, depression, apathy, anxiety, and dementia. Assessments conducted at the same time are important to elucidate risk factors better, as well as the common and different mechanisms underlying those conditions.

4.4. Strengths and Weaknesses of the Study

The first step in arriving at a correct diagnosis of mental health problems is to distinguish delirium from other psychiatric syndromes that can cause confusion, such as dementia, depression, and mania. Evaluating different mental problems concurrently is also important, given the overlap between them. The careful and broad evaluation of mental health symptoms in stroke is a strong side of this study.

In our study, patients with aphasia, a frequent stroke consequence, were not excluded. If it was possible, CAM-ICU was administered; if patients could not be formally tested, then they were strictly observed by ward nurses and raters and the consensus diagnosis was made.

Since it is unclear to what degree previous psychopathology may serve as a risk factor for the development of mental health-problems after in-hospital delirium episode; prior psychiatric illness can influence mental status post-stroke, i.e., represents either recurrence or continuation of a preexisting psychiatric illness, we very carefully excluded patients with pre-morbid mental health problems.

This study included a big number of patients at the baseline that allowed a sustained reasonable big number of patients during all follow-ups.

A variety of raters; neurologist and psychologist assessed patients at baseline and during follow-up visits. This is considered as the strength of this study, because follow-up raters were blind for the patients' previous performance and behavior. On the other hand, patients who are more familiar to assessors are more willing to ask for help if they have problems with understanding the questions from the questionnaire, and therefore provide more adequate answers. Therefore, the variety of raters can be also considered as a weakness of the study.

Some limitations of our study and bias inducers should also be addressed. Firstly, we used questionnaires to describe symptoms of anxiety, depression, apathy and fear that are not diagnostic tools,

as using interviews with a mental health professional was not feasible. Secondly, patients that were lost in the follow-up had more risk factors, which could have had a negative influence on the outcome and been a potential source of bias. Thirdly, as this was a single center study, the generalizability of our results may be limited.

5. Conclusions

The results of this study show, that mental health problems are a very frequent post-stroke complication. Delirium diagnosed in the acute phase of stroke influences the mental health of affected patients. This effect is especially significant in the first months post-stroke and vanishes with time, which suggests that delirium during hospitalization might not be a damaging occurrence in most measures of mental health problems. Apathy seems to be the most connected mental health complication with in-hospital delirium among stroke patients.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/7/2232/s1, Table S1: Prevalence of depression, apathy, anxiety and aggression/hostility in hospital, at 3-month follow-up and 12-month follow-up in no-delirium and delirium groups, Table S2: Influence of post-stroke delirium on the incidence of depression in hospital, at 3-month follow-up and 12-month follow-up in univariate and multivariate logistic regression models, Table S3: Influence of post-stroke delirium on the incidence of apathy in hospital, at 3-month follow-up and 12-month follow-up in univariate and multivariate logistic regression models, Table S4: Influence of post-stroke delirium on the incidence of anxiety in hospital, at 3-month follow-up and 12-month follow-up in univariate and multivariate logistic regression models, Table S5: Influence of post-stroke delirium on the incidence of aggression/hostility in hospital, at 3-month follow-up and 12-month follow-up in univariate and multivariate logistic regression models, Table S6: Influence of post-stroke delirium on the incidence of depression, apathy, anxiety and aggression/hostility in hospital, at 3-month follow-up and 12-month follow-up in univariate and multivariate logistic regression models.

Author Contributions: Conceptualization, A.K.-M.; methodology, K.K., P.P. and A.K.-M.; validation, J.D., A.G. and A.K.-M.; formal analysis, J.D., M.M.; investigation, K.K. and P.P., M.M.; writing—original draft preparation K.K., J.D., M.M., and A.K.-M.; writing—review and editing, A.G. and A.K.-M.; supervision, A.G. and A.K.-M.; project administration, A.K.-M.; funding acquisition, A.K.-M. All authors have read and agreed to the published version of the manuscript.

Funding: Faculty of Medicine of Jagiellonian University Medical College (Leading National Research Centre 2012–2017) funded the collection of data for the study. Grant number KNOW-9000474.

Acknowledgments: We thank Elzbieta Klimiec for data collection.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gustafson, Y.; Olsson, T.; Eriksson, S.; Asplund, K.; Bucht, G. Acute confusional states (delirium) in stroke patients. *Cerebrovasc. Dis.* **1991**, *1*, 257–264. [CrossRef]
2. Alvarez-Perez, F.J.; Paiva, F. Prevalence and Risk Factors for Delirium in Acute Stroke Patients. A Retrospective 5-Years Clinical Series. *J. Stroke Cerebrovasc. Dis.* **2017**, *26*, 567–573. [CrossRef] [PubMed]
3. Shi, Q.; Presutti, R.; Selchen, D.; Saposnik, G. Delirium in acute stroke: A systematic review and meta-analysis. *Stroke* **2012**, *43*, 645–649. [CrossRef] [PubMed]
4. Pasińska, P.; Wilk, A.; Kowalska, K.; Szyper-Maciejowska, A.; Klimkowicz-Mrowiec, A. The long-term prognosis of patients with delirium in the acute phase of stroke: PRospective Observational POLIsh Study (PROPOLIS). *J. Neurol.* **2019**, *266*, 2710–2717. [CrossRef]
5. Mansutti, I.; Saiani, L.; Palese, A. Delirium in patients with ischaemic and haemorrhagic stroke: Findings from a scoping review. *Eur. J. Cardiovasc. Nurs.* **2019**, *18*, 435–448. [CrossRef]
6. Ferro, J.M.; Santos, A.C. Emotions after stroke: A narrative update. *Int. J. Stroke* **2020**, *15*, 256–267. [CrossRef]
7. Davydow, D.S. Symptoms of depression and anxiety after delirium. *Psychosomatics* **2009**, *50*, 309–316. [CrossRef]
8. Inouye, S.K.; Van Dyck, C.H.; Alessi, C.A.; Balkin, S.; Siegal, A.P.; Horwitz, R.I. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Ann. Intern. Med.* **1990**, *113*, 941–948. [CrossRef] [PubMed]

9. Ely, E.W.E.; Inouye, S.K.; Bernard, G.R.; Gordon, S.; Francis, J.; May, L.; Truman, B.; Speroff, T.; Gautam, S.; Margolin, R.; et al. Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* **2001**, *286*, 2703–2710. [CrossRef]
10. Hart, R.P.; Levenson, J.L.; Sessler, C.N.; Best, A.M.; Schwartz, S.M.; Rutherford, L.E. Validation of a cognitive test for delirium in medical ICU patients. *Psychosomatics* **1996**, *37*, 533–546. [CrossRef]
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; (DSM-5); American Psychiatric Association: Philadelphia, PA, USA, 2013.
12. De Groot, V.; Beckerman, H.; Lankhorst, G.J.; Bouter, L.M. How to measure comorbidity. A critical review of available methods. *J. Clin. Epidemiol.* **2003**, *56*, 221–229. [CrossRef]
13. Cummings, J.L.; Mega, M.; Gray, K.; Rosenberg-Thompson, S.; Carusi, D.A.; Gornbein, J. The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology* **1994**, *44*, 2308–2314. [CrossRef] [PubMed]
14. Klimkowicz, A.; Dziedzic, T.; Slowik, A.; Szczudlik, A. Incidence of pre-and poststroke dementia: Cracow stroke registry. *Dement. Geriatr. Cogn. Disord.* **2002**, *14*, 137–140. [CrossRef]
15. Nasreddine, Z.S.; Phillips, N.A.; Bédirian, V.; Charbonneau, S.; Whitehead, V.; Collin, I.; Cummings, J.L.; Chertkow, H. The Montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* **2005**, *53*, 695–699. [CrossRef]
16. Dubois, B.; Slachevsky, A.; Litvan, I.; Pillon, B. The FAB: A Frontal Assessment Battery at bedside. *Neurology* **2000**, *55*, 1621–1626. [CrossRef]
17. Meyer, B.C.; Lyden, P.D. The modified national institutes of health stroke scale: Its time has come. *Int. J. Stroke* **2009**, *4*, 267–273. [CrossRef]
18. Bonita, R.; Beaglehole, R. Recovery of motor function after stroke. *Stroke* **1998**, *19*, 1497–1500. [CrossRef]
19. Kroenke, K.; Spitzer, R.L.; Williams, J.B.W. The PHQ-9: Validity of a Brief Depression Severity Measure. *J. Gen. Intern. Med.* **2001**, *16*, 606–613. [CrossRef] [PubMed]
20. De Man-van Ginkel, J.M.; Gooskensm, F.; Schepers, V.P.; Schuurmans, M.J.; Lindeman, E.; Hafsteinsdóttir, T.B. Screening for poststroke depression using the patient health questionnaire. *Nurs. Res.* **2012**, *61*, 333–341. [CrossRef]
21. Marin, R.S.; Biedrzycki, R.C.; Firinciogullari, S. Reliability and Validity of the Apathy Evaluation Scale. *Psychiatry. Res.* **1991**, *38*, 143–162. [CrossRef]
22. Brodaty, H.; Sachdev, P.S.; Withall, A.; Altendorf, A.; Valenzuela, M.J.; Lorentz, L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke – the Sydney Stroke Study. *Psychol. Med.* **2005**, *35*, 1707–1716. [CrossRef] [PubMed]
23. Spielberger, C.D.; Gorsuch, R.L.; Lushene, P.R.; Vagg, P.R.; Jacobs, G.A. *Manual for the State-Trait. Anxiety Inventory*; Consulting Psychologists Press, Inc.: Palo Alto, CA, USA, 1983.
24. Wrześniewski, K.; Sosnowski, T.; Jaworowska, A.; Fecenec, D. *STAI. State-Trait. Anxiety Inventory. Polish Adaptation STAI*, 4th ed.; Pracownia Testów Psychologicznych Polskiego Towarzystwa Psychologicznego: Warszawa, Poland, 2011.
25. Buss, A.H.; Durkee, A. An inventory for assessing different kinds of hostility. *J. Consult. Psychol.* **1957**, *21*, 343–349. [CrossRef] [PubMed]
26. Stanik, J.M.; Roszkowska, A.; Kucharewicz, J. Psychologiczna diagnoza zachowań agresywnych w świetle badań Skalą Agresji Buss-Durkee (SABD)—Wyniki badań i normalizacja testu. In *Zastosowanie wybranych technik diagnostycznych w psychologicznej praktyce klinicznej i sądowej*; Stanik, J.M., Ed.; Wydawnictwo Uniwersytety Ślaskiego: Katowice, Poland, 2006.
27. Hackett, M.L.; Pickles, K. Part I: Frequency of depression after stroke: An updated systematic review and meta-analysis of observational studies. *Int. J. Stroke.* **2014**, *9*, 1017–1025. [CrossRef]
28. Jorge, R.E.; Starkstein, S.E.; Robinson, R.G. Apathy following stroke. *Can. J. Psychiatry* **2010**, *55*, 350–354. [CrossRef] [PubMed]
29. Knapp, P.; Dunn-Roberts, A.; Sahib, N.; Cook, L.; Astin, F.; Kontou, E.; Thomas, S.A. Frequency of anxiety after stroke: An updated systematic review and meta-analysis of observational studies. *Int. J. Stroke* **2020**, *15*, 244–255. [CrossRef] [PubMed]
30. Ramos-Perdigues, S.; Mané-Santacana, A.; Pintor-Pérez, L. Prevalence and associated factors of anger post stroke: A systematic review. *Rev. Neurol.* **2015**, *60*, 481–489. [CrossRef]
31. Nelson, S.; Rustad, J.K.; Catalano, G.; Stern, T.A.; Kozel, F.A. Depressive Symptoms Before, During, and After Delirium: A Literature Review. *Psychosomatics* **2016**, *57*, 131–141. [CrossRef]

32. Chan, E.K.W.; Shen, Q.; Cordato, D.; Kneebone, I.; Xu, Y.H.; Chan, D.K.Y. Delirium post-stroke: Short- to long-term effect on anxiety and depression compared to effect on cognition. *Top. Stroke. Rehabil.* **2017**, *24*, 597–600. [CrossRef]
33. Kazmierski, J.; Kowman, M.; Banach, M.; Pawelczyk, T.; Okonski, P.; Iwaszkiewicz, A.; Zaslonka, J.; Sobow, T.; Kloszewska, I. Preoperative Predictors of Delirium After Cardiac Surgery: A Preliminary Study. *Gen. Hosp. Psychiatry* **2006**, *28*, 536–538. [CrossRef]
34. Leung, J.M.; Sands, L.P.; Mullen, E.A.; Wang, Y.; Vaurio, L. Are preoperative depressive symptoms associated with postoperative delirium in geriatric surgical patients? *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2005**, *60*, 1563–1568. [CrossRef] [PubMed]
35. McAvay, G.J.; Van Ness, P.H.; Bogardus, S.T., Jr.; Zhang, Y.; Leslie, D.L.; Leo-Summers, L.S.; Inouye, S.K. Depressive symptoms and the risk of incident delirium in older hospitalized adults. *J. Am. Geriatr. Soc.* **2007**, *55*, 684–691. [CrossRef] [PubMed]
36. Marin, R.S. Differential diagnosis and classification of apathy. *Am. J. Psychiatry* **1990**, *147*, 22–30. [CrossRef] [PubMed]
37. Le Heron, C.; Apps, M.A.J.; Husain, M. The anatomy of apathy: A neurocognitive framework for amotivated behaviour. *Neuropsychologia* **2018**, *118*, 54–67. [CrossRef] [PubMed]
38. Cavallari, M.; Dai, W.; Guttmann, C.R.; Meier, D.S.; Ngo, L.H.; Hshieh, T.T.; Callahan, A.E.; Fong, T.G.; Schmitt, E.; Dickerson, B.C.; et al. Neural substrates of vulnerability to postsurgical delirium as revealed by presurgical diffusion MRI. *Brain* **2016**, *139*, 1282–1294. [CrossRef]
39. Yang, S.; Hua, P.; Shang, X.; Cui, Z.; Zhong, S.; Gong, G.; William Humphreys, G. Deficiency of brain structural sub-network underlying post-ischaemic stroke apathy. *Eur. J. Neurol.* **2015**, *22*, 341–347. [CrossRef]
40. Onoda, K.; Kuroda, Y.; Yamamoto, Y.; Abe, S.; Oguro, H.; Nagai, A.; Bokura, H.; Yamaguchi, S. Post-stroke apathy and hypoperfusion in basal ganglia: SPECT study. *Cerebrovasc. Dis.* **2011**, *31*, 6–11. [CrossRef]
41. Dougherty, D.D.; Shin, L.M.; Alpert, N.M.; Pitman, R.K.; Orr, S.P.; Lasko, M.; Macklin, M.L.; Fischman, A.J.; Rauch, S.L. Anger in healthy men: A PET study using script-driven imagery. *Biol. Psychiatry* **1999**, *46*, 466–472. [CrossRef]
42. Paradiso, S.; Robinson, R.G.; Andreasen, N.C.; Downhill, J.E.; Davidson, R.J.; Kirchner, P.T.; Watkins, G.L.; Ponto, L.L.; Hichwa, R.D. Emotional activation of limbic circuitry in elderly normal subjects in a PET study. *Am. J. Psychiatry* **1997**, *154*, 384–389. [CrossRef]

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Early Depression Independently of Other Neuropsychiatric Conditions, Influences Disability and Mortality after Stroke (Research Study—Part of PROPOLIS Study)

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Received: 19 October 2020; Accepted: 15 November 2020; Published: 17 November 2020

Abstract: Post-stroke depression (PSD) is the most frequent neuropsychiatric consequence of stroke. The nature of the relationship between PSD and mortality still remains unknown. One hypothesis is that PSD could be more frequent in those patients who are more vulnerable to physical disability, a mediator variable for higher level of physical damage related to higher risk of mortality. Therefore, the authors' objective was to explore the assumption that PSD increases disability after stroke, and secondly, that mortality is higher among patients with PSD regardless of stroke severity and other neuropsychiatric conditions. We included 524 consecutive patients with acute stroke or transient ischemic attack, who were screened for depression between 7–10 days after stroke onset. Physical impairment and death were the outcomes measures at evaluation check points three and 12 months post-stroke. PSD independently increased the level of disability three (OR = 1.94, 95% CI 1.31–2.87, p = 0.001), and 12 months post-stroke (OR = 1.61, 95% CI 1.14–2.48, p = 0.009). PSD was also an independent risk factor for death three (OR = 5.68, 95% CI 1.58–20.37, p = 0.008) and 12 months after stroke (OR = 4.53, 95% CI 2.06–9.94, p = 0.001). Our study shows the negative impact of early PSD on the level of disability and survival rates during first year after stroke and supports the assumption that depression may act as an independent mediator for disability leading to death in patients who are more vulnerable for brain injury.

Keywords: post-stroke depression; disability level; mortality

1. Introduction

Stroke is not only a leading cause of permanent functional disability, but also often causes severe impairment of mental health. Post-stroke depression (PSD) is the most frequent neuropsychiatric complication of stroke. In the meta-analysis by Hackett and Pickles [1], the pooled data showed that depression was present in 31% of stroke survivors at any time up to five-years post stroke, however its frequency varied across studies from 5% at two to five days after stroke to 84% at three months after

stroke. Our data on PSD, among Polish patients with stroke, showed that PSD occurs in 54.58% of patients at the hospital, in 58.51% three months, and in 54.75% 12 months after the stroke [2].

It is important to recognize that depression is not a normal consequence of stroke, and still a lot of patients with stroke and physical impairment will not develop depression. Depression often coexist with other neuropsychiatric conditions which also increase the risk of negative prognosis, like apathy, anxiety, dementia, or delirium, and which often are misdiagnosed with depression. Sorting them out is essential for both, a correct risk assessment and for proper interventions.

Depressive symptoms occurring early after stroke increase the risk of negative consequences including death [3]. The rate of mortality among patients with PSD differs at different time points after stroke, also different risk factors are identified to increase the risk of death in this population [3–5]. Despite the fact that many studies have dealt with PSD, the nature of the relationship between PSD and mortality remains unknown and requires further analysis in order to draw a convincing conclusion. Among different hypothesis about the relationship between PSD and mortality one states that depression could be more frequent in those patients who are more vulnerable to physical disability [6] and PSD could act as a mediator variable for severe physical damage related to higher risk of mortality. A better understanding of this association would strengthen the evidence for causality, improve the therapeutic approach to patients with PSD, and provide prognostic information on survival. To check this hypothesis, we assumed that PSD negatively influences disability after stroke, regardless of stroke severity, other neuropsychiatric conditions, and higher mortality among patients with PSD.

Therefore, the objective of this study was to assess the change in the level of disability over a year in patients with PSD and their risk of death compared to depression-free patients by controlling other neuropsychiatric conditions and the severity of stroke.

2. Materials and Methods

This study was conducted as part of a larger prospective study, known as the PROPOLIS (PRospective Observational POLIsh Study on post-stroke delirium). Testing took place in the stroke unit at the University Hospital and Outpatient Clinic at the Neurology Department, University Hospital, Krakow. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. Informed written consent was provided by each participant or caregiver. The Local Bioethics Committee of Jagiellonian University approved the study (KBET/63/B/2014).

2.1. Population and Design

The consecutive patients admitted to the Stroke Unit at the University Hospital in Krakow, with stroke (ischemic or hemorrhagic) or transient ischemic attack (TIA) met inclusion criteria (Patients > 18 years of age, admitted within 48 h from the first stroke symptoms, speaking Polish, without serious communication deficits), were included into this sub-study. All patients had neuroimaging (CT/MRI) performed on admission. Stroke was defined as a sudden onset of neurological deficit lasting longer than 24 h. All patients were treated according to standard protocols of international guidelines [7].

Data regarding socio-demographic factors and comorbidities was collected. The Cumulative Illness Rating Scale (CIRS) was used as a general indicator of health status [8]. The severity of clinical deficit after stroke was graded by the National Institutes of Health Stroke Scale (NIHSS) [9] and the disability prior to admission was assessed by the modified Rankin Scale (mRS) [10].

Depression symptoms were assessed between 7 and 10 days after admission with Polish version of Patient Health Questionnaire-9 (PHQ-9) [11]. This questionnaire queries symptoms present using 4-point Likert scale with item scores ranging from 0 (symptoms not present) to 3 (symptoms present nearly every day). The score ranges from 0 (no depressive symptoms) to 27 (all symptoms occurring nearly every day) and can be used to determine depression severity (0–4 indicates no depression,

5–9 mild depression, 10 to 14 moderate depression, 15–19 moderately severe depression and 20–27 severe depression). PHQ-9 shows good reliability, validity and clinical utility when used in stroke patients [12]. Patients enrolled in the study completed the questionnaire on their own or with the help of a psychologist when filling out was impossible or difficult (e.g., the patient could not hold the pen because of a paresis or had a visual impairment). Depression was diagnosed if the patient received 5 or more points on the PHQ-9 scale [13].

To evaluate post-stroke apathy (PSA), the Apathy Evaluation Scale-C (AES-C) [14] was used. AES is an 18-item questionnaire with a clinician rated version that was applied in this study. The questions address patient's activities, interest in doing things, relationship with others and feelings over the past two to three weeks. Each item is rated on a 4-point Likert scale with item scoring ranging from 1 (not at all true) to 4 (very true). The total AES-C score ranges from 18 to 72, with higher scores indicating greater apathy. The AES has good reliability and validity and was frequently used in studies on post-stroke apathy [14]. Apathy was diagnosed with AES score of ≥ 37 points [15].

Anxiety was measured with Polish adaptation of State Trait Anxiety Inventory (STAI) [16,17], the 40-item instrument, measuring, respectively, transient and enduring levels of anxiety. The state scale used in the present study administered as a self-completion questionnaire by the interviewer, assessed how the patients felt at the moment or in the recent past and how they anticipate their feelings to be in a specific, hypothetic situation in the future. The STAI scale is scored on four levels of anxiety intensity from 1 (not at all) to 4 (very much) and with a sum score between 20 and 80. The raw results are interpreted by referring to a relevant sten scores and then categorized into three levels of anxiety: low (1–4 sten), moderate (5–6 sten) and high (7–10 sten) [17].

Patients were screened for delirium with the abbreviated version of Confusion Assessment Method (bCAM) or the Intensive Care Units version (CAM-ICU), specifically in patients with motor aphasia or those who could not communicate for other reasons [18,19]. The final diagnosis of delirium was based on both clinical observation and structural assessment. The diagnostic criteria for delirium were based on the DSM-5 classification [20].

To screen for pre-stroke depression (pre-SD), a member of family/spouse or a close informant of the patient's household filled out the Neuropsychiatric Inventory [21]. In addition, patients were asked about previous treatment for depression, and medical records were checked for antidepressants among the medications currently taken by the patient.

In order to diagnose patients with pre-stroke dementia, a Polish version of Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) was used [22].

2.2. Outcome Assessment

We assessed the following outcome measures: presence of depression between 7–10th day after admission to the hospital, degree of disability in daily activities and mortality after stroke 3 and 12 months after stroke during the follow-up visit. Patients who did not attend a follow-up visit were contacted by phone and the information was gathered. A neurologist and a psychologist, both uninvolved in the baseline assessment of patients, were responsible for data acquisition.

2.3. Statistics

Statistical analysis was performed using Statistica 13.3 software (StatSoft®, Kraków, Poland). Qualitative variables were compared using the chi-squared test with or without Yates' correction, as appropriate. Quantitative values were presented as medians with interquartile ranges (IQRs) and compared with the Mann-Whitney U test due to non-normal distribution in each case. Correlations were statistically evaluated using Pearson's correlation tests and correlation coefficients (r) were obtained.

Associations between PSD (based on the PHQ-9 cut-off point) and 3-month and 12-month mortality were found using univariate logistic regression models. Predictive values were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Similarly, associations between PSD and disability

(increase in mRS of ≥1) were evaluated. Then, multivariate logistic regression models were adjusted for age, gender, and comorbidities (CIRS score). p-values < 0.05 were considered statistically significant.

3. Results

From 750 patients included into PROPOLIS study 524 filled out the PHQ-9. After three and 12 months after stroke 514 and 487 patients were available for examination, respectively. A flowchart (Figure 1) and a timeline (Figure 2) show the study design.

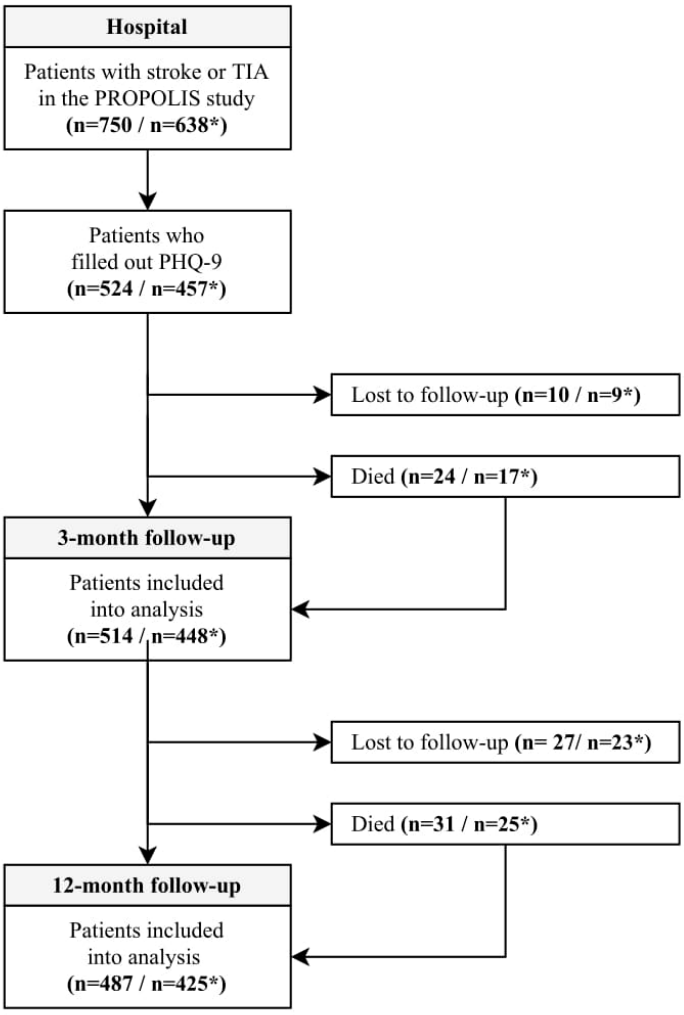

Figure 1. Study flowchart.

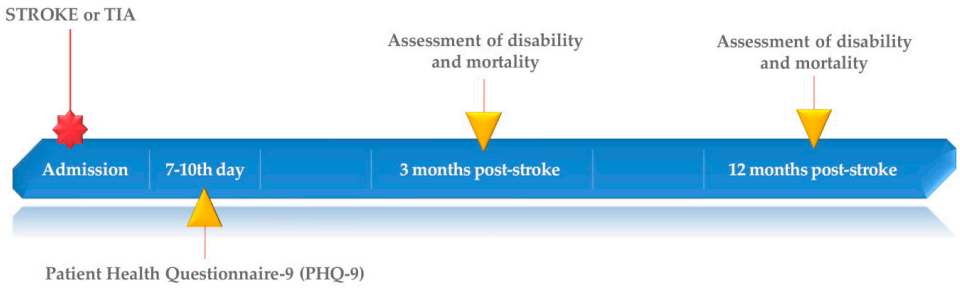

Figure 2. Study timeline.

When compared to controls, patients with PSD were significantly older, more often females, less often had left hemispheres stroke and treatment with recombinant tissue plasminogen activator (rt-PA), suffered from pneumonia, and had higher C-reactive protein (CRP) levels during hospitalization. Also, they were significantly more physically disabled prior to admission, more often had TIA or stroke in the past and had more comorbidities at baseline comparisons. Early depression was significantly more often accompanied by other neuropsychiatric conditions: apathy, anxiety, delirium, and dementia. Table 1 shows the details.

After three months, 24 patients died, 10 were lost from the follow-up and mRS score was not obtained in 18 patients. After 12 months, 31 persons died, and another 27 patients were lost from the follow-up. Patients who were lost from the follow-up did not differ significantly from those analyzed. Table 2 shows the results.

In the first step, we compared patients with PHQ-9 $\geq$ 5 points with those who scored 4 or less. After 3 and 12 months after stroke, PSD was an independent risk factor for death in multivariable logistic regression analysis. Also, PSD independently increased the level of disability of 1 point on mRS among patients with PSD three and 12 months post-stroke. Table 3 and Figures 3 and 4 show the final results.

In the second step, we excluded patients with pre-SD from further analyses. The general characteristic of patients with PSD and controls, after exclusion of patients with pre-SD, are shown in Table 4. The final results were very similar to those obtained in first analysis. Only the side of stroke lost its significance.

In regression analyses, PSD was still an independent variable for mortality and increased level of disability measured by mRS three and 12 months after stroke. Table 5 shows the results.

Patients that were lost from the follow-up in this sub-analysis did not differ significantly from analyzed group. Table 6 shows the details.

In the third step, we compared only pre-SD with patients without depression (pre- or post-stroke). Patients with pre-SD were significantly more often women, had more comorbidities and had higher level of disability prior to admission. Table 7 shows the details.

Pre-SD increased the level of disability on mRS of 1 point at threeand 12 months post-stroke and predicted mortality within 12 months after stroke. Table 8 shows the results.

Patients with pre-SD significantly more often had PSD and they also had significantly more severe depression when compared to other individuals. There was no relationship between NIHSS score and PHQ-9 score. Tables 9 and 10 show the results.

Table 1. Baseline characteristics of patients without and with post-stroke depression in hospital. (All included patients).

Variable	Data	No Depression *n* = 238 (45.42%)	Depression *n* = 286 (54.58%)	*p*-Value
Male gender *	524	143/238 (60.08)	122/286 (42.66)	<0.001
Age [years] **	524	68 (60–78)	71 (62–80)	0.022
Higher education *	518	49/235 (20.85)	49/283 (17.31)	0.306
Length of education [years] **	515	11 (10–14)	11 (10–13)	0.122
Hemorrhagic stroke *	524	12/238 (5.04)	16/286 (5.59)	0.780
TOAST classification:				
- large-artery atherosclerosis *	457	27/210 (12.86)	28/247 (11.34)	0.618
- cardioembolism *	457	11/210 (5.24)	15/247 (6.07)	0.701
- small-vessel occlusion *	457	63/210 (30.00)	79/247 (31.98)	0.648
- other determined etiology *	457	107/210 (50.95)	122/247 (49.39)	0.740
- undetermined etiology *	457	2/210 (0.95)	3/247 (1.21)	0.855
Side of stroke:				
- right hemisphere *	524	93/238 (39.09)	136/286 (47.55)	0.051
- left hemisphere *	524	112/238 (47.06)	105/286 (36.71)	0.017
- posterior part *	524	31/238 (13.03)	35/286 (12.24)	0.787
- more than one localization *	524	2/238 (0.84)	10/286 (3.50)	0.084
rt-Pa treatment *	524	68/238 (28.57)	52/286 (18.18)	0.007
Thrombectomy *	524	12/238 (5.04)	12/286 (4.20)	0.645
Medical history:				
- hypertension *	524	158/238 (66.39)	206/286 (72.03)	0.163
- diabetes *	524	49/238 (20.59)	92/286 (32.17)	0.003
- atrial fibrillation *	524	39/238 (16.39)	54/286 (18.88)	0.457
- myocardial infraction *	524	33/238 (13.87)	40/286 (13.99)	0.968
- PCI or CABG *	524	22/238 (9.24)	25/286 (8.74)	0.841
- smoking—ever *	523	118/237 (49.79)	149/286 (52.10)	0.599
- smoking—current *	523	62/237 (26.16)	86/286 (30.07)	0.323
- previous stroke or TIA *	522	32/237 (13.50)	60/285 (21.05)	0.024
CIRS, total score **	524	7 (5–11)	10 (6–13)	<0.001
Pneumonia *	524	8/238 (3.36)	23/286 (8.04)	0.038
Urinary tract infections *	505	58/232 (25.00)	81/273 (29.67)	0.242
Length of hospital stay [days] **	524	9 (8–10)	9 (8–11)	0.320
Aphasia in hospital *	524	53/238 (22.27)	50/286 (17.48)	0.170
Neglect in hospital *	524	22/238 (9.24)	34/286 (11.89)	0.329
Vision deficits in hospital *	524	59/238 (24.79)	89/286 (31.12)	0.109
Delirium in hospital*	524	25/238 (10.50)	66/286 (23.08)	<0.001
AES score at 7–10th day in hospital **	480	29 (20–38)	34 (25–43)	<0.001
STAI-S score at 7–10th day in hospital **	520	32 (27–39)	42 (33–52)	<0.001
STAI-T score at 7–10th day in hospital **	519	35 (30–41.5)	47 (40–54)	<0.001
NIHSS at admission **	524	4 (2–8)	4 (2–9)	0.649
Pre-hospital mRS **	524	0 (0–0)	0 (0–1)	0.002
Pre-hospital IQCODE **	436	78 (78–79)	78 (78–83)	0.007
CRP level in hospital [mg/l] **	507	3.82 (1.63–10.34)	5.75 (2.04–18.60)	0.003

* *n* (%); ** median (IQR); TOAST—Trial of Org 10172 in Acute Stroke Treatment; rt-Pa—recombinant tissue plasminogen activator; PCI—percutaneous coronary interventions; CABG—coronary artery bypass graft; TIA—transient ischemic attack; CIRS—Cumulative Illness Rating Scale; AES—Apathy Evaluation Scale; STAI—State-Trait Anxiety Inventory (S—state scale, T—trait scale); NIHSS—National Institutes of Health Stroke Scale; mRS—Modified Rankin Scale; IQCODE—Informant Questionnaire on Cognitive Decline in the Elderly; CRP—C-reactive protein.

Table 2. Comparison of analyzed and lost to follow-up cases. (All included patients).

Variable	Data	Analyzed Cases	Lost to Follow-Up	*p*-Value
Comparison of Analyzed (*n* = 514) and Lost to Follow-Up (*n* = 10) Cases for 3-Month Mortality				
Male gender *	524	259/514 (50.39)	6/10 (60.00)	0.777
Age (years) **	524	69 (61–79)	69.5 (62–77)	0.581
CIRS, total score **	524	8.5 (5–12)	7 (5–10)	0.441
NIHSS at admission **	524	4 (2–9)	3 (0–10)	0.428
Pre-hospital mRS **	524	0 (0–0)	0 (0–0)	0.834
Comparison of Analyzed (*n* = 496) and Lost to Follow-Up (*n* = 28) Cases for 3-Month mRS				
Male gender *	524	250/496 (50.40)	15/28 (53.57)	0.744
Age (years) **	524	69 (61–79)	71 (62–79.5)	0.662
CIRS, total score **	524	9 (5–12)	7.5 (5–11.5)	0.374
NIHSS at admission **	524	4 (2–9)	3 (0–7)	0.113
Pre-hospital mRS **	524	0 (0–0)	0 (0–0.5)	0.858
Comparison of Analyzed (*n* = 487) and Lost to Follow-Up (*n* = 37) Cases for 12-Month Mortality and mRS				
Male gender *	524	244/487 (50.10)	21/37 (56.76)	0.435
Age (years) **	524	69 (61–79)	71 (63–78)	0.639
CIRS, total score **	524	9 (5–12)	7 (4–11)	0.130
NIHSS at admission **	524	4 (2–8)	4 (2–12)	0.317
Pre-hospital mRS **	524	0 (0–0)	0 (0–0)	0.871

* *n* (%); ** median (IQR); CIRS—Cumulative Illness Rating Scale; NIHSS—National Institutes of Health Stroke Scale; mRS—Modified Rankin Scale.

Table 3. Influence of post-stroke depression on mortality and disability 3 and 12 months after stroke. (All included patients).

		Incidence, *n* (%)		Univariate Logistic Regression Model		Multivariate Logistic Regression Model *	
Variable	**Data**	**No Depression**	**Depression**	**OR (95CI)**	***p*-Value**	**OR (95CI)**	***p*-Value**
3 months:							
Mortality	514	3/234 (1.28)	21/280 (7.50)	6.243 (1.838–21.204)	0.003	5.685 (1.586–20.378)	0.008
Increase in mRS of ≥1	496	121/228 (53.07)	191/268 (71.27)	2.194 (1.514–3.179)	<0.001	1.944 (1.315–2.876)	0.001
12 months:							
Mortality	487	9/220 (4.09)	46/267 (17.23)	4.880 (2.331–10.216)	<0.001	4.535 (2.065–9.964)	<0.001
Increase in mRS of ≥1	487	112/220 (50.91)	178/267 (66.67)	1.929 (1.336–2.783)	<0.001	1.681 (1.141–2.478)	0.009

* adjusted for age, gender and CIRS (Cumulative Illness Rating Scale); mRS—Modified Rankin Scale.

Table 4. Baseline characteristics of patients without and with post-stroke depression in hospital. (Only patients without Pre-Stroke Depression).

Variable	Data	No Depression *n* = 223 (48.80%)	Depression *n* = 234 (51.20%)	*p*-Value
Male gender *	457	139/223 (62.33)	104/234 (44.44)	<0.001
Age (years) **	457	67 (60–78)	73 (62–80)	0.011
Higher education *	451	47/220 (21.36)	40/231 (17.32)	0.276
Length of education (years) **	449	12 (10–14)	11 (9–13)	0.064
Hemorrhagic stroke *	457	12/223 (5.38)	12/234 (5.13)	0.904
TOAST classification:				
- large-artery atherosclerosis *	398	24/197 (12.18)	22/201 (10.95)	0.699
- cardioembolism *	398	11/197 (5.58)	11/201 (5.47)	0.961
- small-vessel occlusion *	398	59/197 (29.95)	65/201 (32.34)	0.607
- other determined etiology *	398	101 (51.27)	101/201 (50.25)	0.839
- undetermined etiology *	398	2/197 (1.02)	2/201 (1.00)	0.630
Side of stroke:				
- right hemisphere *	457	88/223 (39.46)	108/234 (46.15)	0.149
- left hemisphere *	457	102/223 (45.74)	88/234 (37.61)	0.079
- posterior part *	457	31/223 (13.90)	30/234 (12.82)	0.734
- more than one localization *	457	2/223 (0.90)	8/23 (3.42)	0.128
rt-Pa treatment *	457	61/223 (27.35)	41/234 (17.52)	0.012
Thrombectomy *	457	11/223 (4.93)	9/234 (3.85)	0.570
Medical history:				
- hypertension *	457	148/223 (66.37)	172/234 (73.50)	0.096
- diabetes *	457	44/223 (19.73)	76/234 (32.48)	0.002
- atrial fibrillation *	457	35/223 (15.70)	44/234 (18.80)	0.380
- myocardial infraction *	457	32/223 (14.35)	32/234 (13.68)	0.836
- PCI or CABG *	457	22/223 (9.87)	20/234 (8.55)	0.626
- smoking—ever *	456	112/222 (50.45)	118/234 (50.43)	0.996
- smoking—current *	456	59/222 (26.58)	66/234 (28.21)	0.697
- previous stroke or TIA *	455	30/222 (13.51)	49/233 (21.03)	0.036
CIRS, total score **	457	7 (4–11)	9 (6–12)	<0.001
Pneumonia *	457	7/223 (3.14)	21/234 (8.97)	0.009
Urinary tract infections *	442	52/218 (23.85)	68/224 (30.36)	0.124
Length of hospital stay [days] **	457	9 (8–10)	9 (8–11)	0.472
Aphasia in hospital *	457	48/223 (21.52)	40/234 (17.09)	0.230
Neglect in hospital *	457	20/223 (8.97)	28/234 (11.97)	0.296
Vision deficits in hospital *	457	53/223 (23.77)	71/234 (30.34)	0.114
Delirium in hospital *	457	20/223 (8.97)	53/234 (22.65)	<0.001
AES score at 7–10th day in hospital **	411	28 (20–36)	32.5 (24–42)	<0.001
STAI-S score at 7–10th day in hospital **	453	31 (27–39)	41 (32–51)	<0.001
STAI-T score at 7–10th day in hospital **	452	35 (30–41)	45 (39–53)	<0.001
NIHSS at admission **	457	4 (2–7)	4 (2–9)	0.673
Pre-hospital mRS **	457	0 (0–0)	0 (0–1)	0.003
Pre-hospital IQCODE **	377	78 (78–79)	78 (78–81)	0.019
CRP level in hospital [mg/L] **	442	3.74 (1.59–10.77)	5.44 (1.97–17.25)	0.010

* *n* (%); ** median (IQR); TOAST—Trial of Org 10172 in Acute Stroke Treatment; rt-Pa—recombinant tissue plasminogen activator; PCI—percutaneous coronary interventions; CABG—coronary artery bypass graft; TIA—transient ischemic attack; CIRS—Cumulative Illness Rating Scale; AES—Apathy Evaluation Scale; STAI—State-Trait Anxiety Inventory (S—state scale, T—trait scale); NIHSS—National Institutes of Health Stroke Scale; mRS—Modified Rankin Scale; IQCODE—Informant Questionnaire on Cognitive Decline in the Elderly; CRP—C-reactive protein.

Table 5. Influence of post-stroke depression on mortality and disability 3 and 12 months after stroke. (Only patients without Pre-stroke depression).

		Incidence, *n* (%)		Univariate Logistic Regression Model		Multivariate Logistic Regression Model *	
Variable	**Data**	**No Depression**	**Depression**	**OR (95CI)**	***p*-Value**	**OR (95CI)**	***p*-Value**
3 months:							
Mortality	448	3/219 (1.37)	14/229 (6.11)	4.688 (1.328–16.548)	0.016	4.447 (1.184–16.707)	0.027
Increase in mRS of ≥1	432	109/213 (51.17)	151/219 (68.95)	2.119 (1.431–3.137)	<0.001	1.856 (1.227–2.806)	0.003
12 months:							
Mortality	425	9/208 (4.33)	33/217 (15.21)	3.966 (1.847–8.512)	<0.001	3.712 (1.644–8.381)	0.002
Increase in mRS of ≥1	425	104/208 (50.00)	140/217 (64.52)	1.818 (1.232–2.682)	0.003	1.588 (1.056–2.387)	0.026

* adjusted for age, gender and CIRS (Cumulative Illness Rating Scale); mRS—Modified Rankin Scale.

Table 6. Comparison of analyzed and lost to follow-up cases. (Only patients without Pre-Stroke Depression).

Variable	**Data**	**Analyzed Cases**	**Lost to Follow-Up**	***p*-Value**
Comparison of Analyzed (*n* = 448) and Lost to Follow-Up (*n* = 9) Cases for 3-Month Mortality				
Male gender *	457	237/448 (52.90)	5/9 (66.67)	0.629
Age (years) **	457	69.5 (61–79)	68 (62–71)	0.366
CIRS, total score **	457	8 (5–12)	6 (5–10)	0.276
NIHSS at admission **	457	4 (2–8)	3 (0–10)	0.496
Pre-hospital mRS **	457	0 (0–0)	0 (0–0)	0.991
Comparison of Analyzed (*n* = 432) and Lost to Follow-Up (*n* = 25) Cases for 3-Month mRS				
Male gender *	457	229/432 (53.01)	14/25 (56.00)	0.771
Age (years) **	457	69 (61–79)	71 (62–78)	0.909
CIRS, total score **	457	8 (5–12)	6 (5–10)	0.278
NIHSS at admission **	457	4 (2–8)	3 (0–7)	0.216
Pre-hospital mRS **	457	0 (0–0)	0 (0–1)	0.573
Comparison of Analyzed (*n* = 425) and Lost to Follow-Up (*n* = 32) Cases for 12-Month Mortality and mRS				
Male gender *	457	223/425 (52.47)	20/32 (62.50)	0.273
Age (years) **	457	69 (61–79)	69.5 (62–78)	0.874
CIRS, total score **	457	8 (5–12)	7 (3–11)	0.122
NIHSS at admission **	457	4 (2–8)	4 (2–12)	0.364
Pre-hospital mRS **	457	0 (0–0)	0 (0–0)	0.575

* *n* (%); ** median (IQR); CIRS—Cumulative Illness Rating Scale; NIHSS—National Institutes of Health Stroke Scale; mRS—Modified Rankin Scale.

Table 7. Baseline characteristics of patients without depression and with pre-stroke depression.

Variable	Data	No Depression *n* = 223 (79.08%)	Pre-Stroke Depression *n* = 59 (20.92%)	*p*-Value
Male gender *	282	139/223 (62.33)	20/59 (33.90)	<0.001
Age (years) **	282	67 (60–78)	68 (61–79)	0.302
Previous stroke or TIA *	281	30/222 (13.51)	13/59 (22.03)	0.106
CIRS, total score **	282	7 (4–11)	11 (6–15)	<0.001
NIHSS at admission **	282	4 (2–7)	5 (2–11)	0.264
Pre-hospital mRS **	282	0 (0–0)	0 (0–1)	0.034

* *n* (%); ** median (IQR); TIA—transient ischemic attack; CIRS—Cumulative Illness Rating Scale; NIHSS—National. Institutes of Health Stroke Scale; mRS—Modified Rankin Scale.

Table 8. Influence of pre-stroke depression on mortality and disability 3 and 12 months after stroke.

		Incidence, *n* (%)		Univariate Logistic Regression Model		Multivariate Logistic Regression Model *	
Variable	**Data**	**No Depression**	**Pre-Stroke Depression**	**OR (95CI)**	***p*-Value**	**OR (95CI)**	***p*-Value**
3 months:							
Mortality	277	3/219 (1.37)	6/58 (10.34)	8.308 (2.011–34.322)	0.003	2.414 (0.376–15.497)	0.353
Increase in mRS of ≥1	270	109/213 (51.17)	47/57 (82.46)	4.484 (2.153–9.338)	<0.001	3.965 (1.826–8.610)	<0.001
12 months:							
Mortality	264	9/208 (4.33)	12/56 (21.43)	6.030 (2.394–15.191)	<0.001	3.406 (1.064–10.904)	0.039
Increase in mRS of ≥1	264	104/208 (50.00)	42/56 (75.00)	3.000 (1.546–5.823)	0.001	2.395 (1.171–4.897)	0.017

* adjusted for age, gender and CIRS (Cumulative Illness Rating Scale); mRS—Modified Rankin Scale.

Table 9. Association of incidence of pre-stroke depression with post-stroke depression and median PHQ-9 score.

Variable	Data	Pre-Stroke Depression *n* = 59 (20.92%)	No Pre-Stroke Depression *n* = 457 (88.57%)	*p*-Value
Post-stroke depression *	516	48/59 (81.36)	234/457 (51.20)	<0.001
PHQ-9 score **	516	9 (6–12)	5 (2–9)	<0.001

* *n* (%); ** median (IQR); PHQ-9—The Patient Health Questionnaire-9.

Table 10. Correlations between NIHSS and PHQ-9 at the hospital.

Group	Data	Pearson's Correlation Coefficient (r)	*p*-Value
All patients	524	−0.0128	0.770
Pre-stroke depression excluded	457	−0.0384	0.413

NIHSS—National Institutes of Health Stroke Scale; PHQ-9—The Patient Health Questionnaire-9.

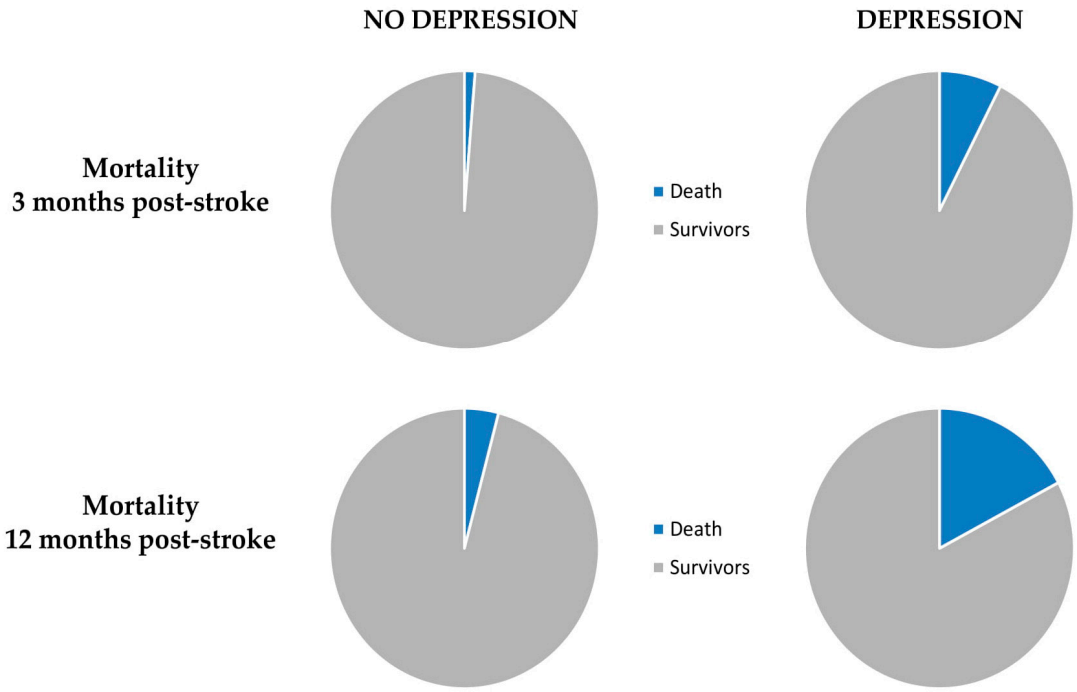

Figure 3. A pie chart presenting the influence of post-stroke depression on mortality.

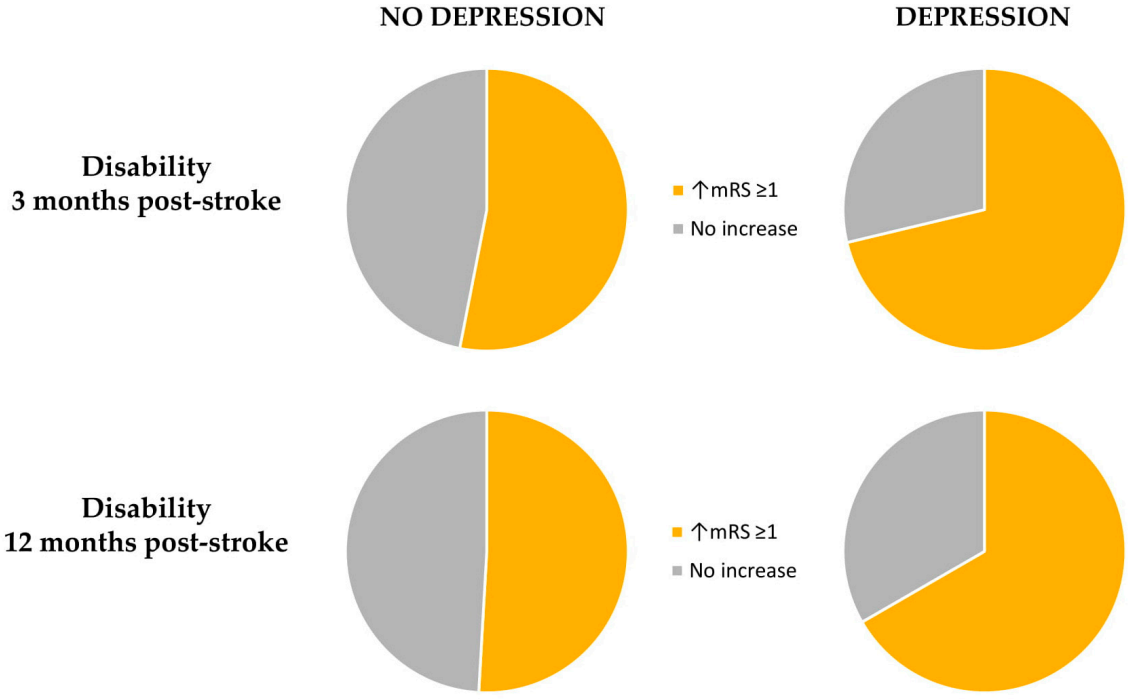

Figure 4. A pie chart presenting the influence of post-stroke depression on disability.

4. Discussion

In our cohort, depression was diagnosed in 54.58% of patients between seven and 10 days after stroke. Patients who developed depressive symptoms in acute phase of stroke had about six times higher risk of death three months after stroke and nearly 4.5 times higher risk after 12 months, when compared to patients without depression. PSD negatively influenced level of disability and mortality rate at three and 12 months after stroke. Both outcomes were independent from stroke severity and concomitant neuropsychiatric conditions.

Other studies have also reported an association between PSD and mortality after stroke. In study by Williams et al. [23], among total of 51,119 patients hospitalized with an ischemic stroke, those diagnosed with PSD had a higher three-year mortality risk, even despite being younger and having fewer chronic conditions. Previous meta-analysis [4–6], also showed that mortality was an independent outcome of depression after stroke and patients with early PSD had a risk of death about 1.5 higher as compared with non-depressed individuals, considering both short- and long-term mortality. In a study by Razmara et al. [24], the combination of depression and stroke was associated with all—cause mortality, with the highest risk of death in those aged 65–74 years. Patients with depressive symptoms were about 35 times more likely to die when compared to stroke survivors without depression.

Our study found that PSD increases the level of disability both three and 12 months after stroke. In earlier studies [25,26], depressed patients have been found more dependent in activities of daily living at three and 15-month follow-up than patients without depression. Paolucci et al. [27] estimated that PSD is a relevant factor that is responsible for about 15% of the increased disability observed in post—stroke depressive patient.

As was shown, pre-SD was associated with higher stroke morbidity and mortality [28]. In our cohort, pre-SD was independently related to increased mortality 12 months post-stroke but not three months. The number of patients with pre-SD was small which can explain this lack of association for the three-month observation.

Pre-SD, which is due to many factors, e.g., social, degenerative, or vascular, also negatively influenced the level of disability both three and 12 months after stroke. Results of this study suggest, that regardless of etiology, depression increases negative outcomes after stroke.

The association between stroke and depression is well established as well as between stroke and poor functional outcome. The connecting factor between depression, physical impairment, and mortality in patients with stroke can be brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, involved in neuronal development, differentiation, and survival.

There is a general agreement that etiology of mood disorders is multifactorial. Hypotheses about the participation and interrelationship of down regulation of neurotrophins, inflammation, hypothalamic-pituitary-adrenal axis hyperactivity and stress in pathophysiology of depression have an important support in literature [29].

Recent findings have reported that BDNF is a key regulator in the neuro-immune axis regulation, but its potential mechanism in depression remains unclear [30]. Lower BDNF levels were found to be a significant risk factor for PSD [31] as well as in clinically depressed individuals [32]. BDNF could intermediate between depression and the level of disability after stroke. Stroke activates microglia, which are brain guards and the first non-neuronal cells to respond to various acute brain injuries [33]. An inflammatory state can contribute to the development and progression of depression pathology, influencing alterations of the neuroplasticity caused by reduced BDNF expression, activity, and affinity to a receptor [30,34,35]. Moreover, BDNF levels are mediated by physical exercise enhancing its levels in the brain [36]. Activity-driven increases in BDNF have also been shown to promote motor recovery after stroke [37]. Physical rehabilitation may be impaired by depressions, and depressed patients are less likely to exercise what lowers the level of BDNF and intensify functional impairment. For the time being, there is not enough evidence of a definitive link between BDNF and depression, disability and mortality, and their potential interrelationships need to be confirmed in future studies.

Immunological mechanisms, as mentioned, are implicated in the pathogenesis of depressive symptoms. C-reactive protein is the inflammatory biomarker, an acute phase protein that increases in level during the acute phase of inflammation. Patients with depression exhibit increased peripheral blood concentrations of CRP [38,39]. Elevated CRP along with other peripheral blood markers of inflammation have been found to predict development of depression [40] and resistance to antidepressant therapy [41]. A few studies have examined the relationship between circulating CRP and risk of post-stroke depression with conflicting results [42–44]. In the previous sub-study, we found that this association was significant for depression diagnosed during hospitalization, but there was no association between depression diagnosed three months post-stroke and CRP levels [45]. Interestingly, in this present, much larger study, patients with depression, diagnosed at the hospital, had significantly higher level of CRP than dementia-free patients, thus supporting the hypothesis of the role of immunological mechanisms in development of depressive symptoms.

In the pathophysiology of depression, a dysregulated kynurenine pathway has also been implicated. In this pathway, tryptophan is broken down into kynurenine and then to neurotoxic quinolinic acid and decreases the availability of tryptophan for serotonin synthesis. The altered levels of kynurenines have been implicated in psychiatric [46] and neurodegenerative diseases [47]. Preliminary data from one small study among patients with stroke also suggest that the kynurenine pathway may be implicated in PSD and disability [48]. Kynurenic acid seems to be useful not only in process of diagnosis but also in prediction of the treatment response [49].

Research shows that inflammation is an important, multi-directional factor in the etiology of depression, but further research is still needed on its role in diagnosing depression, guiding decision making on clinical treatment and monitoring the course of the disease and the risk of its relapse.

Strengths and Weaknesses of the Study

The first step in arriving at a correct diagnosis of mental health problems is to distinguish depression from other psychiatric syndromes that can cause confusion, such as delirium, dementia, apathy, or anxiety. Evaluating different mental problems concurrently is also important to distinguish between the right diagnoses, given the overlap between them. Careful and broad evaluation of mental health problems at the hospital is a strong side of PROPOLIS.

Prior psychiatric illness can influence mental status post-stroke, i.e., represents either recurrence or continuation of a preexisting psychiatric illness. Therefore, in PROPOLIS, we carefully screened for neuro-psychiatric conditions including depression, dementia, delirium, anxiety, and apathy pre-stroke.

This study had prospective design and included a large number of patients at the baseline, which helped to sustain a reasonably large number of patients during all follow-ups. Patients that were lost in the follow-up didn't differ significantly from those followed-up.

A variety of raters; neurologist and psychologist assessed patients at baseline and during follow-up visits. This is considered as the strength of this study, because follow-up raters were blind for the patients' previous performance and behavior. On the other hand, patients who are more familiar to assessors are more willing to ask for help if they have problems with understanding the questions from the questionnaire and therefore provide more adequate answers. Therefore, a variety of raters can be also considered as a weakness of the study.

Some limitations of our study and bias inducers should also be addressed. Firstly, the PROPOLIS was designed to determine frequency, predictors, and clinical consequences of post-stroke delirium. Depressive symptoms were considered as a secondary endpoint of the study. Secondly, we used questionnaires to describe symptoms of depression, since using interviews with mental health professional was not feasible. Thirdly, the first evaluation for depressive disorders took place before the 14th day after stroke, which may have overestimated the prevalence of depression in the acute phase of stroke. Fourthly, during the follow-up visits, we observed, most depressed patients did not have formal diagnosis of depression and were not treated, but data on the treatment with antidepressants were not collected during the follow-ups. Because treatment with antidepressants might influence the study

outcome, this is considered as a limitation. Fifth, as this was a single center study, the generalizability of our results may be limited.

5. Conclusions

Depression can act as a mediator variable for a higher disability level and mortality in patients more vulnerable to brain injury, independently of other neuropsychiatric mental health problems.

A high prevalence of depression after stroke should stress the need for future research exploring its possible pathomechanism and testing, if an early management of depression may change life expectancy after stroke and improve the outcome, even if functional deficits remain.

Author Contributions: Conceptualization, K.K. and A.K.-M.; methodology, K.K., P.P. and A.K.-M.; validation, K.K., Ł.K., J.D., A.W. and A.K.-M.; formal analysis, K.K., Ł.K. and A.W.; investigation, K.K. and P.P.; writing—original draft preparation, K.K. and A.K.-M.; writing—review and editing, J.D., Ł.K., A.W., P.P. and A.K.-M.; supervision A.K.-M.; project administration, A.K.-M.; funding acquisition, A.K.-M. All authors have read and agreed to the published version of the manuscript.

Funding: Faculty of Medicine of Jagiellonian University Medical College (Leading National Research Centre 2012–2017) funded the collection of data for the study. Grant number KNOW-9000474.

Acknowledgments: We thank Małgorzata Mazurek for manuscript editing, and Elżbieta Klimiec for data collection.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hackett, M.L.; Pickles, K. Part I: Frequency of depression after stroke: An updated systematic review and meta-analysis of observational studies. *Int. J. Stroke* **2014**, *9*, 1017–1025. [CrossRef]
2. Kowalska, K.; Droś, J.; Mazurek, M.; Pasińska, P.; Gorzkowska, A.; Klimkowicz-Mrowiec, A. Delirium Post-Stroke: Short- and Long-Term Effect on Depression, Anxiety, Apathy and Aggression (Research Study—Part of PROPOLIS Study). *J. Clin. Med.* **2020**, *9*, 2232. [CrossRef]
3. Bartoli, F.; Di Brita, C.; Crocamo, C.; Clerici, M.; Carrà, G. Early Post-stroke Depression and Mortality: Meta-Analysis and Meta-Regression. *Front. Psychiatry* **2018**, *9*, 530. [CrossRef]
4. Ayerbe, L.; Ayis, S.; Wolfe, C.D.A.; Rudd, A.G. Natural history, predictors and outcomes of depression after stroke: Systematic review and meta-analysis. *Br. J. Psychiatry* **2013**, *202*, 14–21. [CrossRef]
5. Bartoli, F.; Lillia, N.; Lax, A.; Crocamo, C.; Mantero, V.; Carra, G.; Agostini, E.; Clerici, M. Depression after Stroke and Risk of Mortality: A Systematic Review and Meta-Analysis. *Stroke Res. Treat.* **2013**, *2013*, 862978. [CrossRef]
6. Hackett, M.L.; Anderson, C.S. Predictors of depression after stroke: A systematic review of observational studies. *Stroke* **2005**, *36*, 2296–2301. [CrossRef]
7. Intercollegiate Stroke Working Party. *National Clinical Guideline for Stroke*, 4th ed.; Royal College of Physicians: London, UK, 2012.
8. de Groot, V.; Beckerman, H.; Lankhorst, G.J.; Bouter, L.M. How to measure comorbidity. a critical review of available methods. *J. Clin. Epidemiol.* **2003**, *56*, 221–229. [CrossRef]
9. Meyer, B.C.; Lyden, P.D. The modified national institutes of health stroke scale: Its time has come. *Int. J. Stroke* **2009**, *4*, 267–273. [CrossRef] [PubMed]
10. Broderick, J.P.; Adeoye, O.; Elm, J. Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. *Stroke* **2017**, *48*, 2007–2012. [CrossRef]
11. Tomaszewski, K.; Zarychta, M.; Bieńkowska, A.; Chmurowicz, E.; Nowak, W.; Skalska, A. Validation of the Patient Health Questionnaire-9 Polish version in the hospitalised elderly population. *Psychiatr. Pol.* **2011**, *45*, 223–233.
12. de Man-van Ginkel, J.M.; Gooskensm, F.; Schepers, V.P.; Schuurmans, M.J.; Lindeman, E.; Hafsteinsdóttir, T.B. Screening for poststroke depression using the patient health questionnaire. *Nurs. Res.* **2012**, *61*, 333–341. [CrossRef] [PubMed]
13. Kroenke, K.; Spitzer, R.L.; Williams, J.B.W. The PHQ-9: Validity of a Brief Depression Severity Measure. *J. Gen. Intern. Med.* **2001**, *16*, 606–613. [CrossRef] [PubMed]

14. Marin, R.S.; Biedrzycki, R.C.; Firinciogullari, S. Reliability and Validity of the Apathy Evaluation Scale. *Psychiatry Res.* **1991**, *38*, 143–162. [CrossRef]
15. Brodaty, H.; Sachdev, P.S.; Withall, A.; Altendorf, A.; Valenzuela, M.J.; Lorentz, L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke—The Sydney Stroke Study. *Psychol. Med.* **2005**, *35*, 1707–1716. [CrossRef]
16. Spielberger, C.D.; Gorsuch, R.L.; Lushene, P.R.; Vagg, P.R.; Jacobs, G.A. *Manual for the State-Trait Anxiety Inventory*; Consulting Psychologists Press, Inc.: Palo Alto, CA, USA, 1983.
17. Wrześniewski, K.; Sosnowski, T.; Jaworowska, A.; Fecenec, D. *STAI. State-Trait Anxiety Inventory. Polish Adaptation STAI*, 4th ed.; Pracownia Testów Psychologicznych Polskiego Towarzystwa Psychologicznego: Warszawa, Poland, 2011.
18. Inouye, S.K.; Van Dyck, C.H.; Alessi, C.A.; Balkin, S.; Siegal, A.P.; Horwitz, R.I. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Ann. Intern. Med.* **1990**, *113*, 941–948. [CrossRef]
19. Ely, E.W.E.; Inouye, S.K.; Bernard, G.R.; Gordon, S.; Francis, J.; May, L.; Truman, B.; Speroff, T.; Gautam, S.; Margolin, R.; et al. Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* **2001**, *286*, 2703–2710. [CrossRef] [PubMed]
20. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; DSM-5; American Psychiatric Association: Arlington, MA, USA, 2013.
21. Cummings, J.L.; Mega, M.; Gray, K.; Rosenberg-Thompson, S.; Carusi, D.A.; Gornbein, J. The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology* **1994**, *44*, 2308–2314. [CrossRef] [PubMed]
22. Klimkowicz, A.; Dziedzic, T.; Slowik, A.; Szczudlik, A. Incidence of pre-and poststroke dementia: Cracow stroke registry. *Dement. Geriatr. Cogn. Disord.* **2002**, *14*, 137–140. [CrossRef]
23. Williams, L.S.; Ghose, S.S.; Swindle, R.W. Depression and other mental health diagnoses increase mortality risk after ischemic stroke. *Am. J. Psych.* **2004**, *161*, 1090–1095. [CrossRef]
24. Razmara, A.; Valle, N.; Markovic, D.; Sanossian, N.; Ovbiagele, B.; Dutta, T.; Towfighi, A. Depression Is Associated with a Higher Risk of Death among Stroke Survivors. *J. Stroke Cerebrovasc. Dis.* **2017**, *26*, 2870–2879. [CrossRef]
25. Pohjasvaara, T.; Vataja, R.; Leppävuori, A.; Kaste, M.; Erkinjuntti, T. Depression is an independent predictor of poor long-term functional outcome post-stroke. *Eur. J. Neurol.* **2001**, *8*, 315–319. [CrossRef]
26. Pohjasvaara, T.; Leppävuori, A.; Siira, I.; Vataja, R.; Kaste, M.; Erkinjuntti, T. Frequency and clinical determinants of poststroke depression. *Stroke* **1998**, *29*, 2311–2317. [CrossRef]
27. Paolucci, S.; Iosa, M.; Coiro, P.; Venturiero, V.; Savo, A.; De Angelis, D.; Morone, G. Post-stroke Depression Increases Disability More Than 15% in Ischemic Stroke Survivors: A Case-Control Study. *Front. Neurol.* **2019**, *10*, 926. [CrossRef]
28. Pan, A.; Sun, Q.; Okereke, O.I.; Rexrode, K.M.; Hu, F.B. Depression and risk of stroke morbidity and mortality: A meta-analysis and systematic review. *JAMA* **2011**, *306*, 1241–1249. [CrossRef]
29. Verduijn, J.; Milaneschi, Y.; Schoevers, R.A.; van Hemert, A.M.; Beekman, A.T.F.; Penninx, B.W.J.H. Pathophysiology of major depressive disorder: Mechanisms involved in etiology are not associated with clinical progression. *Transl. Psychiatry* **2015**, *5*, e649. [CrossRef]
30. Jin, Y.; Sun, L.H.; Yang, W.; Cui, R.J.; Xu, S.B. The role of BDNF in the neuroimmune axis regulation of mood disorders. *Front. Neurol.* **2019**, *10*, 515. [CrossRef]
31. Noonan, K.; Carey, L.M.; Crewther, S.G. Meta-analyses indicate associations between neuroendocrine activation, deactivation in neurotrophic and neuroimaging markers in depression after stroke. *J. Stroke Cerebrovasc. Dis.* **2013**, *22*, e124–e135. [CrossRef]
32. Bocchio-Chiavetto, L.; Bagnardi, V.; Zanardini, R.; Molteni, R.; Nielsen, M.G.; Placentino, A.; Giovannini, C.; Rillosi, L.; Ventriglia, M.; Riva, M.A.; et al. Serum and plasma BDNF levels in major depression: A replication study and meta-analyses. *World J. Biol. Psychiatry* **2010**, *11*, 763–773. [CrossRef]
33. Lan, X.; Liu, R.; Sun, L.; Zhang, T.; Du, G. Methyl salicylate 2-O-β-D-lactoside, a novel salicylic acid analogue, acts as an anti-inflammatory agent on microglia and astrocytes. *J. Neuroinflammation* **2011**, *8*, 98. [CrossRef]
34. Pariante, C.M. Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. *Eur. Neuropsychopharmacol.* **2017**, *27*, 554–559. [CrossRef]

35. Wohleb, E.S.; Franklin, T.; Iwata, M.; Duman, R.S. Integrating neuroimmune systems in the neurobiology of depression. *Nat. Rev. Neurosci.* **2016**, *17*, 497–511. [CrossRef] [PubMed]
36. Bathina, S.; Das, U.N. Brain-derived neurotrophic factor and its clinical implications. *Arch. Med. Sci.* **2015**, *11*, 1164–1178. [CrossRef] [PubMed]
37. Clarkson, A.N.; Overman, J.J.; Zhong, S.; Mueller, R.; Lynch, G.; Carmichael, S.T. AMPA receptor-induced local brain-derived neurotropic factor signaling mediates motor recovery after stroke. *J. Neurosci.* **2011**, *31*, 3766–3775. [CrossRef] [PubMed]
38. Howren, M.B.; Lamkin, D.M.; Suls, J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosom. Med.* **2009**, *71*, 171–186. [CrossRef]
39. Haapakoski, R.; Mathieu, J.; Ebmeier, K.P.; Alenius, H.; Kivimaki, M. Cumulative meta-analysis of interleukins 6 and 1beta, tumour necrosis factor alpha and C-reactive protein in patients with major depressive disorder. *Brain Behav. Immun.* **2015**, *49*, 206–215. [CrossRef]
40. Gimeno, D.; Kivimaki, M.; Brunner, E.J.; Elovainio, M.; De Vogli, R.; Steptoe, A.; Kumari, M.; Lowe, G.D.O.; Rumley, A.; Marmot, M.G.; et al. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychol. Med.* **2009**, *39*, 413–423. [CrossRef]
41. Strawbridge, R.; Arnone, D.; Danese, A.; Papadopoulos, A.; Herane Vives, A.; Cleare, A.J. Inflammation and clinical response to treatment in depression: A meta-analysis. *Eur. Neuropsychopharmacol.* **2015**, *25*, 1532–1543. [CrossRef]
42. Jiménez, I.; Sobrino, T.; Rodríguez-Yáñez, M.; Pouso, M.; Cristobo, I.; Sabucedo, M.; Blanco, M.; Castellanos, M.; Leira, R.; Castillo, J. High serum levels of leptin are associated with post-stroke depression. *Psychol. Med.* **2009**, *39*, 1201–1209. [CrossRef]
43. Yang, R.R.; Lu, B.C.; Li, T.; Du, Y.F.; Wang, X.; Jia, Y.X. The relationship between high-sensitivity C-reactive protein at admission and post stroke depression: A 6-month follow-up study. *Int. J. Geriatr. Psychiatry* **2016**, *31*, 231–239. [CrossRef]
44. Cheng, L.S.; Tu, W.J.; Shen, Y.; Zhang, L.J.; Ji, K. Combination of high-sensitivity C-reactive protein and homocysteine predicts the post-stroke depression in patients with ischemic stroke. *Mol. Neurobiol.* **2018**, *55*, 2952–2958. [CrossRef]
45. Kowalska, K.; Pasińska, P.; Klimiec-Moskal, E.; Pera, J.; Słowik, A.; Klimkowicz-Mrowiec, A.; Dziedzic, T. C-reactive protein and post-stroke depressive symptoms. *Sci. Rep.* **2020**, *10*, 1431. [CrossRef] [PubMed]
46. Hunt, C.; Macedo e Cordeiro, T.; Suchting, R.; de Dios, C.; Cuellar Leal, V.A.; Soares, J.C.; Dantzer, R.; Teixeira, A.L.; Selvaraj, S. Effect of immune activation on the kynurenine pathway and depression symptoms—A systematic review and meta-analysis. *Neurosci. Biobeha. Rev.* **2020**, *118*, 514–523. [CrossRef] [PubMed]
47. Tanaka, M.; Toldi, J.; Vécsei, L. Exploring the Etiological Links behind Neurodegenerative Diseases: Inflammatory Cytokines and Bioactive Kynurenines. *Int. J. Mol. Sci.* **2020**, *21*, 2431. [CrossRef] [PubMed]
48. Carrillo-Mora, P.; Pérez-De la Cruz, V.; Estrada-Cortés, B.; Toussaint-González, P.; Martínez-Cortéz, J.A.; Rodríguez-Barragán, M.; Quinzaños-Fresnedo, J.; Rangel-Caballero, F.; Gamboa-Coria, G.; Sánchez-Vázquez, I.; et al. Serum Kynurenines Correlate with Depressive Symptoms and Disability in Poststroke Patients: A Cross-sectional Study. *Neurorehabilit. Neural Repair* **2020**, *34*, 936–944. [CrossRef] [PubMed]
49. Erabi, H.; Okada, G.; Shibasaki, C.; Setoyama, D.; Kang, D.; Takamura, M.; Yoshino, A.; Fuchikami, M.; Kurata, A.; Kato, T.A.; et al. Kynurenic acid is a potential overlapped biomarker between diagnosis and treatment response for depression from metabolome analysis. *Sci. Rep.* **2020**, *10*, 16822. [CrossRef] [PubMed]

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C-reactive protein and post-stroke depressive symptoms

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Our study aimed to explore the association between serum C-reactive protein (CRP) and post-stroke depressive symptoms. We prospectively recruited 572 patients with ischemic stroke or transient ischemic attack in whom serum CRP level was measured within 48 h after stroke onset. Depressive symptoms were assessed at day 8 and 3 months after stroke in 405 and 306 patients, respectively. Patients with greater depressive symptoms at day 8 and patients with greater depressive symptoms 3 months after stroke had higher CRP level (median: 7.9 vs 4.3 mg/L, $P < 0.01$ and 6.7 vs 3.4 mg/L, $P = 0.01$, respectively). In the univariate analysis, CRP > 9.2 mg/L was associated with depressive symptoms at day 8 (OR: 2.06, 95%CI: 1.30–3.28, $P < 0.01$) and CRP > 4.3 mg/L was associated with depressive symptoms 3 months after stroke (OR: 1.79, 95%CI: 1.06–3.02, $P = 0.03$). In the multivariate analysis, higher CRP level was related to depressive symptoms at day 8 (OR: 2.23, 95%CI: 1.28–3.90, $P < 0.01$), but not depressive symptoms 3 months after stroke (OR: 1.13, 95%CI: 0.59–2.17, $P = 0.71$). In conclusion, higher levels of CRP are associated with greater depressive symptoms at day 8 after stroke, but their effects on depressive symptoms 3 months after stroke are less significant.

Mounting evidence indicates that peripheral inflammation might contribute to the pathophysiology of major depressive disorder (MDD)[1–3]. Animal studies demonstrate that systemic inflammation might interact with the mechanisms important for depression such as, neurotransmitter metabolism, glucocorticoid receptor resistance, and neuronal plasticity[4]. Clinical studies show that circulating markers of immune activation, including cytokines, chemokines, and acute-phase proteins, are observed in the blood of individuals with MDD. The most replicated findings, confirmed by several meta-analyses, pertain to raised C-reactive protein (CRP) and interleukin-6 in a subset of MDD patients[5–8].

About 30% of patients develop depression at any time point up to 5 years after stroke[9,10]. Post-stroke depression is associated with worse functional outcome and increased mortality[11].

In contrast to MDD, the role of systemic inflammation in the pathobiology of post-stroke depression is not well defined. Systemic inflammatory reaction accompanies ischemic stroke. This reaction includes two components: low-grade inflammation that is related to stroke risk factors and comorbidities (e.g. atherosclerosis, hypertension, diabetes mellitus, heart failure or ischemic heart disease) and acute-phase reaction triggered by brain injury and exacerbated by post-stroke infections. As a result, blood levels of interleukin-6 and CRP rise during the first few days after stroke onset[12]. Since post-stroke systemic inflammation could be a potential therapeutic target[13], a better understanding of relationships between peripheral inflammation and depression is clinically important.

Our study aimed to explore the association between circulating CRP and post-stroke depressive symptoms.

Methods

Patient selection and clinical assessment. Patients recruited to this study were selected from persons who participated in the PROPOLIS study (PRospective Observational POLIsh Study on post-stroke delirium). PROPOLIS was a prospective study conducted in the Department of Neurology, University Hospital, Krakow, Poland[14]. The main aim of the PROPOLIS was to determine the frequency, risk factors and prognosis of post-stroke delirium. Participants were recruited to this study between May 2014 and March 2016.

The inclusion criteria to the current sub-study on depressive symptoms were: (1) ischemic stroke or transient ischemic attack (TIA); (2) serum CRP measurement within 48 h after stroke onset; and (3) informed patient's consent. The exclusion criteria were: (1) the pre-stroke diagnosis of major depressive disorder (retrieved from medical records) and (2) hemorrhagic stroke.

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The Bioethics Committee of Jagiellonian University approved the study's protocol. Each patient gave informed consent. All methods were performed in accordance with approved guidelines and regulations.

The presence of depressive symptoms was assessed at day 8 ± 1 and 3 months after stroke onset using the Patient Health Questionnaire (PHQ-9)[15,16]. Previous studies showed that PHQ-9 is a valid and clinically feasible depression screening tool for stroke[17]. Score $\geq$10 was considered indicative of greater depressive symptoms[18,19]. The PHQ-9 was administrated face-to-face by a trained neurologist or psychologist. Before the PHQ-9 administration, aphasia was examined using clinical methods that assessed speech fluency and content, comprehension, and naming. Patients who were not able to understand questions were excluded from the study.

The Neuropsychiatric Inventory (NPI) was used to assess neuropsychiatric disturbances occurring within the 4 weeks before admission. The NPI-Q10 subscale includes 10 behavioural items: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behaviour[20,21]. A score for each item (from zero to 12) is a product of severity scale (from zero to 3) and frequency scale (from zero to 4).

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) with a cut-off of 3.3 was used to diagnose a pre-stroke cognitive decline[22,23]. The IQCODE consists of 26 items that rate change in patients' intellectual abilities over the past 10 years[24].

The core features of delirium were examined using the Brief Confusion Assessment Method[25].

National Institute of Health Stroke Scale (NIHSS) was used to assess neurological deficit on admission[26]. A score of zero means normal function and higher scores indicate greater impairment. The total score ranges from zero to 42.

Laboratory assays. Serum CRP level was quantified via the immunoturbidometric method (Roche Diagnostics, Mannheim, Germany). The assay detection limit was 1 mg/L.

Statistical analysis. The χ^2 test was used to compare proportions, while the Mann–Whitney *U*-test was used to compare continuous variables between groups. Logistic regression was used to determine the predictors of functional outcome. Variables with $P < 0.05$ in the univariate analysis were included in a multivariate analysis. The Box-Tidwell test was used to check the linearity of the logit for the continuous independent variables in logistic regression analysis. The receiver operating characteristic curves were used to identify an optimal cut-off level of CRP that differentiates patients with greater depressive symptoms from those with lower depressive symptoms. Since CRP level could raise within 48 h after stroke onset and its level measured within 12 h might be lower than its level measured between 24–48 h[12], two sensitivity analyses were performed. In the first, the patients in whom the CRP level was measured within 12 h after stroke were excluded. In the second analysis, only patients with CRP measurement within 24 h after stroke were included. The calculations were performed using the program STATISTICA for Windows (version 12.5, Statsoft, Poland).

Results

Of 750 patients that participated in the PROPOLIS study, 572 patients had an ischemic stroke or TIA and the CRP measurement within 48 h after stroke onset. After the exclusion of patients who died or were not able to perform PHQ-9, depressive symptoms were assessed in 405 patients at day 8 and in 306 patients 3 months after stroke (Fig. 1).

Depressive symptoms at day 8. Of 405 included patients (median age: 70, IQs: 61–80; 51.6% women; median NIHSS: 4, IQs: 2–9), greater depressive symptoms were diagnosed in 104 patients (25.7%).

Compared to patients with lower depressive symptoms, patients with greater depressive symptoms were more often women; suffered from hypertension, previous stroke, and pre-stroke cognitive decline; took antidepressants before index stroke; and had higher pre-stroke NPI score (Table 1). Serum CRP level was higher in patients with greater depressive symptoms.

In the univariate analysis, CRP level above 9.2 mg/L was associated with greater depressive symptoms (OR: 2.06, 95%CI: 1.30–3.28, $P < 0.01$). In the multivariate analysis adjusted for hypertension, female sex, previous stroke, pre-stroke cognitive decline, the use of anti-depressant before stroke, and the NPI score, CRP level remained the independent predictor of depression (OR: 2.23, 95%CI: 1.28–3.90, $P < 0.01$). Other independent predictors of greater depressive symptoms were: female sex (OR: 2.97, 95%CI: 1.67–5.29, $P < 0.01$), previous stroke (OR: 2.08, 95%CI: 1.08–4.01, $P = 0.03$), the NPI score (OR: 1.05, 95%CI: 1.02–1.08, $P < 0.01$) and the use of anti-depressant before stroke (OR: 6.07, 95%CI: 1.14–32.17, $P = 0.03$).

Depressive symptoms 3 months after stroke onset. Of 306 included patients (median age: 69, IQs: 61–79; 50.6% women; median NIHSS: 4, IQs: 2–8), greater depressive symptoms were diagnosed in 82 patients (26.8%).

Compared to patients with lower depressive symptoms, patients with greater depressive symptoms more often suffered from hypertension, diabetes mellitus, and post-stroke delirium; took antidepressants during 3 months after stroke onset; and had higher pre-stroke NPI score (Table 2). Serum CRP level was higher in patients with greater depressive symptoms.

In the univariate analysis, CRP level above 4.3 mg/L was associated with greater depressive symptoms (OR: 1.79, 95%CI: 1.06–3.02, $P = 0.03$). This association was nonsignificant in the multivariate analysis adjusted for hypertension, diabetes mellitus, delirium, the use of antidepressant and the NPI score (OR: 1.13, 95%CI: 0.59–2.17, $P = 0.71$). The independent predictors of greater depressive symptoms in this model were: hypertension (OR: 2.81, 95%CI: 1.27–6.20, $P = 0.01$), diabetes mellitus (OR: 2.13, 95%CI: 1.08–4.19, $P = 0.03$), and the use of antidepressant (OR: 4.36, 95%CI: 1.96–9.69, $P < 0.01$).

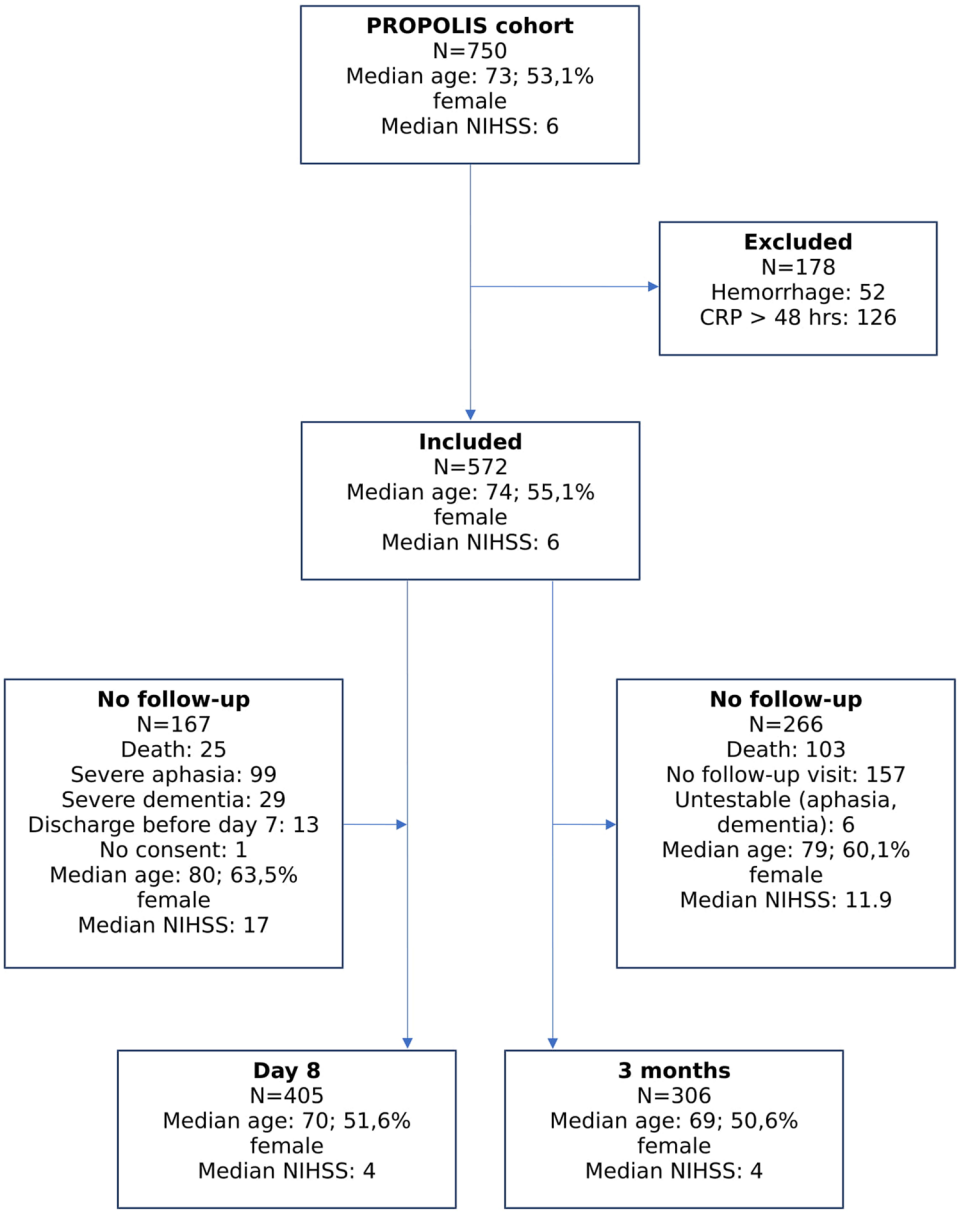

Figure 1. Flow chart showing the numbers of patients included in the study and the reasons for non-inclusion of excluded patients. NIHSS: National Institute of Health Stroke Scale.

When patients treated with anti-depressants were excluded from the analysis, CRP was still associated with depressive symptoms in the univariate (OR: 2.00, 95%CI: 1.10–3.62, P = 0.02), but not in the multivariate analysis (OR: 1.04, 95%CI: 0.50–2.16, P = 0.92).

Sensitivity analysis. In the first sub-analysis, we excluded patients in whom serum CRP level was measured within 12 h after stroke onset (N = 113). Compared to patients with lower depressive symptoms, patients with greater depressive symptoms at day 8 (median: 7.6, interquartiles: 2.1–25.5 mg/L vs median: 4.6, interquartiles: 1.9–11.2 mg/L, P = 0.02) and patients with greater depressive symptoms 3 months after stroke (median: 6.7, interquartiles: 2.7–19.1 mg/L vs median: 3.7, interquartiles: 1.6–11.1 mg/L, P = 0.02) had higher CRP level. In the univariate analysis, serum CRP level above 19.0 mg/L was associated with higher depressive symptoms at day 8 (OR: 2.45, 95%CI: 1.50–4.00, P < 0.01). Similarly, serum CRP level above 4.3 mg/L was related to higher depressive symptoms 3 months after stroke (OR: 2.14, 95%CI: 1.33–3.44, P < 0.01). In the multivariate analysis, higher CRP level remained an independent predictor of depressive symptoms at day 8 (OR: 2.13, 95%CI: 1.18–3.82, P = 0.01), but not depressive symptoms assessed 3 months after stroke (OR: 1.53, 95%CI: 0.86–2.73, P = 0.14).

In the second sub-analysis, we included only patients in whom CRP level was measured within 24 h after stroke onset (N = 292). Compared to patients with lower depressive symptoms, patients with greater depressive symptoms at day 8 (median: 9.2, interquartiles: 2.5–17.2 mg/L vs median: 4.3, interquartiles: 2.1–10.3 mg/L,

	High score of depressive symptoms (N = 104)	Low score of depressive symptoms (N = 301)	P value
Age, median (IQs)	73 (61–82)	69 (61–80)	0.20
Female, n (%)	68 (65.4)	141 (46.8)	<0.01
Hypertension, n (%)	81 (77.9)	204 (67.8)	0.05
Diabetes mellitus, n (%)	33 (31.7)	73 (24.2)	0.13
Atrial fibrillation, n (%)	24 (23.1)	48 (15.9)	0.10
Myocardial infarction, n (%)	17 (16.3)	40 (13.3)	0.44
Previous stroke or TIA, n (%)	27 (26.0)	44 (14.6)	<0.01
Pre-stroke dependency, n (%)	11 (10.6)	19 (6.3)	0.15
Pre-stroke cognitive decline, n (%)*	21/87 (24.1)	33/249 (13.2)	0.02
Pre-stroke total NPI score, median (IQs)**	4.5 (0–14.5)	0 (0–6)	<0.01
Pre-stroke NPI score for depression, median (IQs)**	0 (0–2)	0 (0–0)	<0.01
Pre-stroke use of antidepressants	6 (5.8)	4 (1.3)	0.01
NIHSS score on admission, n (%)	4 (2–9)	4 (2–9)	0.90
Pneumonia, n (%)	8 (7.7)	16 (5.3)	0.38
Urinary tract infections, n (%)	33 (31.7)	82 (27.2)	0.52
Delirium, n (%)	22 (21.1)	49 (16.3)	0.26
Stroke location, n (%)			0.07
Right hemisphere	53 (51.0)	129 (42.9)	
Left hemisphere	35 (33.6)	132 (43.8)	
Posterior fossa	11 (10.6)	37 (12.3)	
Multiple locations	5 (4.8)	3 (1.0)	
Intravenous thrombolysis, n (%)	22 (21.1)	82 (27.2)	0.22
Mechanical thrombectomy, n (%)	6 (5.8)	17 (5.6)	0.96
CRP (mg/L),median (IQs)	7.9 (2.4–20.5)	4.3 (2.1–10.8)	<0.01

Table 1. Baseline characteristics of patients with high and patients with low depressive symptoms score at day 8. *Data available for 336 patients. **Data available for 333 patients.

$P < 0.01$) had higher CRP level. CRP level did not differ ($P = 0.15$) between patients who had greater depressive symptoms 3 months after stroke (median: 6.7, interquartiles: 2.5–11.2 mg/L) compared to patients who had lower depressive symptoms (median: 3.9, interquartiles: 2.1–11.0 mg/L). In the univariate analysis, serum CRP level above 9.17 mg/L was associated with higher depressive symptoms at day 8 (OR: 2.49, 95%CI: 1.45–4.29, $P < 0.01$) and CRP level above 6.7 mg/dL was associated with higher depressive symptoms 3 months after stroke (OR: 2.81, 95%CI: 0.99–3.31, $P = 0.05$). In the multivariate analysis, higher CRP level remained an independent predictor of depressive symptoms at day 8 (OR: 2.89, 95%CI: 1.47–5.69, $P < 0.01$), but not depressive symptoms assessed 3 months after stroke (OR: 1.21, 95%CI: 0.56–2.60, $P = 0.62$).

Discussion

Our study revealed that higher levels of CRP are associated with greater depressive symptoms at day 8 after stroke, but their effects on depressive symptoms 3 months after stroke are less significant.

A few studies have examined the relationship between circulating CRP and risk of post-stroke depression. These studies yielded conflicting results. Jimenez *et al*. measured the serum CRP level in 134 patients with first-ever ischemic stroke[27]. Blood was collected at discharge (day 7 ± 2) and 1 month after stroke. About 19% of patients were diagnosed as having major depression at discharge according to DSM-IV criteria and 22% of patients had major depression 1 month after stroke. The authors did not find any association between CRP level and the risk of post-stroke depression. The study of Yang *et al*. included 226 ischemic stroke patients[28]. CRP level was measured within 24 h after stroke onset. Six months after stroke major depression was diagnosed in 30.5% of patients. In this study, serum CRP level above 0.85 mg/dL was associated with the increased risk of depression after adjusting for potential confounders. Similarly, Cheng *et al*. found that higher CRP level measured with 24 h after stroke onset predicts the increased risk of depression 1 year after stroke[29].

The contribution of inflammatory factors to the pathogenesis of post-stroke depressive symptoms might be dependent on time after stroke. Depressive symptoms that occur very early after stroke onset could be a part of so-called sickness behaviour. Sickness behaviour is a set of behavioural and motivational changes triggered by acute infection or tissue injury and includes anhedonia, hyperalgesia, fever, anorexia, sleepiness, anxiety, and disinterest in social interactions[30,31]. Animal studies have demonstrated that systemic inflammation might induce both sickness behaviour and depressive-like symptoms[30]. Multiple symptoms, for example weight loss, anorexia, fatigue, hyperalgesia, anhedonia, anxiety, and neurocognitive symptoms are shared by both sickness behaviour and depression. Clinical studies involving cancer patients treated with interferon-alpha (INFα) shed light on cytokine-induced sickness behaviour and depressive symptoms. These studies have shown that somatic and

	High score of depressive symptoms (N = 82)	Low score of depressive symptoms (N = 224)	P value
Age, median (IQs)	70.5 (63–78)	68 (60–79)	0.30
Female, n (%)	47 (57.3)	108 (48.2)	0.16
Hypertension, n (%)	68 (82.9)	150 (67.0)	0.01
Diabetes mellitus, n (%)	34 (41.5)	49 (21.9)	<0.01
Atrial fibrillation, n (%)	16 (19.5)	40 (17.9)	0.74
Myocardial infarction, n (%)	12 (14.6)	30 (13.4)	0.78
Previous stroke or TIA, n (%)	16 (19.5)	38 (17.0)	0.20
Pre-stroke dependency, n (%)	8 (9.8)	12 (5.4)	0.17
Pre-stroke cognitive decline, n (%)	13/67 (19.4)	22/191 (11.5)	0.10
Pre-stroke total NPI score, median (IQs) **	3.5 (0–12)	1 (0–7)	0.03
Pre-stroke NPI score for depression, median (IQs)**	0 (0–0)	0 (0–0)	0.94
Pre-stroke use of antidepressants	3 (3.7)	2 (0.9)	0.09
NIHSS score on admission, n (%)	5 (2–10)	4 (2–8)	0.07
Pneumonia, n (%)	8 (9.8)	12 (5.4)	0.17
Urinary tract infections, n (%)	28 (34.1)	52 (23.2)	0.06
Delirium, n (%)	22 (26.8)	27 (12.0)	<0.01
Stroke location, n (%)			0.57
Right hemisphere	39 (47.6)	83 (37.0)	
Left hemisphere	33 (40.2)	110 (49.2)	
Posterior fossa	9 (11.0)	29 (12.9)	
Multiple locations	1 (1.2)	2 (0.9)	
Intravenous thrombolysis, n (%)	26 (31.7)	59 (26.3)	0.35
Mechanical thrombectomy, n (%)	7 (8.5)	15 (6.7)	0.58
Use of anti-depressants 3 months after stroke	19 (23.2)	22 (9.8)	<0.01
CRP (mg/L),median (IQs)	6.7 (2.5–18.1)	3.4 (1.9–10.0)	0.01

Table 2. Baseline characteristics of patients with high and patients with low depressive symptoms score at day 90. *Data available for 258 patients. **Data available for 255 patients.

vegetative symptoms appeared within 2 weeks of INFα therapy[32]. In contrast, mood and cognitive symptoms appeared later during INFα therapy and were more apparent in patients who developed major depression. The hypothesis that early-onset post-stroke depressive symptoms might be related to sickness behaviour is supported by the observation that stroke patients with early-onset (in-hospital) depression had higher frequency of vegetative (anxiety, loss of energy, morning depression, early awakening, weight loss) and melancholic (loss of interest, depressed mood, psychomotor retardation) symptoms compared to patients with late-onset depression[33]. Alternatively, early-onset post-stroke depression might represent a specific phenotype of depression with dominant somatic (vegetative) symptoms rather than sickness behaviour. Further studies with dimensional analyses of specific clusters of neuropsychiatric and somatic symptoms are needed to better characterize the relationship between sickness behaviour and post-stroke depressive symptoms. Differentiation of early depressive symptoms related to sickness behaviour from those predicting major depression could have therapeutic implications. In patients treated with INFα, mood and cognitive symptoms were more responsive, whereas vegetative symptoms, such as anorexia or fatigue, were less responsive to paroxetine treatment[32].

In the univariate analysis, higher CRP was associated with greater depressive symptoms 3 months after stroke. This association was, however, non-significant after adjusting for potential confounders. Inflammatory markers decline gradually after stroke[13]. For this reason, the remote effect of inflammation on depressive symptoms could be weaker than in the acute phase of the stroke. Moreover, the persistence of depressive symptoms beyond the acute phase of stroke might require additional vulnerabilities, including unresolved inflammation, genetic predisposition, or alteration in neuronal networks responsible for mood regulation. We cannot exclude the possibility that our study had too low statistical power to detect an association between CRP and depressive symptoms occurring 3 months after stroke. It should also be noted that inflammatory markers might be selectively associated with only specific dimensions of depression. In MDD, circulating inflammatory markers are especially linked to atypical depression characterized by increased appetite and weight gain[34].

There are several limitations to our study. First, the PROPOLIS was designed to determine frequency, predictors and clinical consequences of post-stroke delirium. Depressive symptoms were considered as a secondary end-point of the study and statistical power was not calculated a priori to check if the study was able to detect an association between CRP and depressive symptoms. Second, no formal psychiatric diagnosis of depression was made. Instead, we used a validated questionnaire to assess depressive symptoms. Third, the CRP level was measured only once. Repeated measurements of inflammatory parameters at different time points after stroke could give better insight into relationships between inflammation and depression. Fourth, about 27% of patients

who were examined in acute stroke did not attend a control visit. These patients were older and had a more severe neurological deficit on admission. Fifth, about 13% of our patients took anti-depressants 3 months after stroke. CRP can interact with anti-depressive medication. In MDD patients, the elevated CRP level was associated with treatment resistance[35].

There are also some advantages to our work. These include the prospective design of the study and assessment of pre-stroke psychiatric symptoms and cognitive decline.

Observational studies are not able to demonstrate if an association between CRP and depressive symptoms is causative. To verify this association, we need an interventional study that will examine if the anti-inflammatory treatment will reduce post-stroke depressive symptoms. From a clinical perspective, depression that occurs early after stroke (e.g., during the first 2 weeks after stroke onset) is associated with long-term poor functional outcome[36,37]. Thus, anti-inflammatory strategies attenuating systemic inflammatory reaction could have a beneficial effect on stroke outcome.

In conclusion, higher levels of serum CRP are associated with early depressive symptoms after ischemic stroke.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Received: 8 August 2019; Accepted: 15 January 2020;
Published online: 29 January 2020

References

1. Wohleb, E. S., Franklin, T., Iwata, M. & Duman, R. S. Integrating neuroimmune systems in the neurobiology of depression. *Nat. Rev. Neurosci.* **17**, 497–511 (2016).
2. Miller, A. H. & Raison, C. L. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat. Rev. Immunol.* **16**, 22–34 (2016).
3. Krishnadas, R. & Cavanagh, J. Depression: an inflammatory illness? *J. Neurol. Neurosurg. Psychiatry.* **83**, 495–502 (2012).
4. Miller, A. H., Maletic, V. & Raison, C. L. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol. Psychiatry.* **65**, 732–741 (2009).
5. Howren, M. B., Lamkin, D. M. & Suls, J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom. Med.* **71**, 171–186 (2009).
6. Valkanova, V., Ebmeier, K. P. & Allan, C. L. CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. *J. Affect. Disord.* **150**, 736–744 (2013).
7. Haapakoski, R., Mathieu, J., Ebmeier, K. P., Alenius, H. & Kivimäki, M. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain. Behav. Immun.* **49**, 206–15 (2015).
8. Fernandes, B. S. *et al.* C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis. *The Lancet Psychiatry.* **3**, 1147–1156 (2016).
9. Ayerbe, L., Ayis, S., Wolfe, C. D. A. & Rudd, A. G. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. *Br. J. Psychiatry.* **202**, 14–21 (2013).
10. Hackett, M. L. & Pickles, K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int. J. Stroke.* **9**, 1017–1025 (2014).
11. Robinson, R. G. & Jorge, R. E. Post-stroke depression: a review. *Am. J. Psychiatry.* **173**, 221–231 (2016).
12. Dziedzic, T. Clinical significance of acute phase reaction in stroke patients. *Front. Biosci.* **13**, 2922–2927 (2008).
13. Dziedzic, T. Systemic inflammation as a therapeutic target in acute ischemic stroke. *Expert Rev. Neurother.* **15**, 523–531 (2015).
14. Klimiec, E. *et al.* PRospective Observational POLIsh Study on post-stroke delirium (PROPOLIS): methodology of hospital-based cohort study on delirium prevalence, predictors and diagnostic tools. *BMC Neurol.* **15**, 94 (2015).
15. Kroenke, K., Spitzer, R. L. & Williams, J. B. The PHQ-9: validity of a brief depression severity measure. *J. Gen. Intern. Med.* **16**, 606–613 (2001).
16. Tomaszewski, K. *et al.* [Validation of the Patient Health Questionnaire-9 Polish version in the hospitalised elderly population]. *Psychiatr Pol.* **45**, 223–233 (2011).
17. Burton, L.-J. & Tyson, S. Screening for mood disorders after stroke: a systematic review of psychometric properties and clinical utility. *Psychol. Med.* **45**, 29–49 (2015).
18. Williams, L. S. *et al.* Performance of the PHQ-9 as a screening tool for depression after stroke. *Stroke.* **36**, 635–638 (2005).
19. de Man-van Ginkel, J. M. *et al.* In-hospital risk prediction for post-stroke depression. *Stroke.* **44**, 2441–2445 (2013).
20. Cummings, J. L. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology.* **48**, S10–16 (1997).
21. Bidzan, L. & Bidzan, M. [Reliability of the Neuropsychiatric Inventory-Nursing Homes Polish version]. *Psychiatr Pol.* **39**, 1219–1229 (2005).
22. Jorm, A. F. & Korten, A. E. Assessment of cognitive decline in the elderly by informant interview. *Br. J. Psychiatry.* **152**, 209–213 (1988).
23. Harrison, J. K. *et al.* Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the diagnosis of dementia within a secondary care setting. *Cochrane Database Syst. Rev.* CD010772; https://doi.org/10.1002/14651858.CD010772.pub2 (2015).
24. Klimkowicz, A., Dziedzic, T., Slowik, A. & Szczudlik, A. Incidence of pre- and poststroke dementia: cracow stroke registry. *Dement Geriatr Cogn Disord.* **14**, 137–140 (2002).
25. Han, J. H. *et al.* Diagnosing delirium in older emergency department patients: validity and reliability of the delirium triage screen and the brief confusion assessment method. *Ann Emerg Med.* **62**, 457–465 (2013).
26. Brott, T. *et al.* Measurements of acute cerebral infarction: a clinical examination scale. *Stroke.* **20**, 864–870 (1989).
27. Jiménez, I. *et al.* High serum levels of leptin are associated with post-stroke depression. *Psychol. Med.* **39**, 1201–1209 (2009).
28. Yang, R. *et al.* The relationship between high-sensitivity C-reactive protein at admission and post stroke depression: a 6-month follow-up study. *Int. J. Geriatr. Psychiatry.* **31**, 231–239 (2016).
29. Cheng, L.-S., Tu, W.-J., Shen, Y., Zhang, L.-J. & Ji, K. Combination of high-sensitivity C-reactive protein and homocysteine predicts the post-stroke depression in patients with ischemic stroke. *Mol. Neurobiol.* **55**, 2952–2958 (2018).
30. Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W. & Kelley, K. W. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* **9**, 46–56 (2008).
31. Maes, M. *et al.* Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Med.* **10**, 66, https://doi.org/10.1186/1741-7015-10-66 (2012).
32. Capuron, L. *et al.* Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology.* **26**, 643–652 (2002).

33. Tateno, A., Kimura, M. & Robinson, R. G. Phenomenological characteristics of poststroke depression: early- versus late-onset. *Am. J. Geriatr. Psychiatry.* **10**, 575–582 (2002).
34. Lamers, F. *et al*. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Mol. Psychiatry.* **18**, 692–699 (2013).
35. Chamberlain, S. R. *et al*. Treatment-resistant depression and peripheral C-reactive protein. *Br. J. Psychiatry.* **214**, 11–19 (2019).
36. Parikh, R. M. *et al*. The impact of poststroke depression on recovery in activities of daily living over a 2-year follow-up. *Arch. Neurol.* **47**, 785–789 (1990).
37. Kang, H.-J. *et al*. Impact of acute phase depression on functional outcomes in stroke patients over 1 year. *Psychiatry Res.* **267**, 228–231 (2018).

Acknowledgements

This study was supported by the grant from National Science Center (2015/19/B/NZ4/00287).

Author contributions

A.K.-M., J.P. and T.D. prepared study protocol. E.K.-M., K.K. and P.P. collected the data. T.D. and A.K.-M. supervised the study. K.K. and T.D. wrote the manuscript. A.K.-M., J.P. and A.S. revised the manuscript for intellectual content.

Competing interests

The authors declare no competing interests.

Additional information

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V. Streszczenie

Celem pierwszej pracy była ocena wpływu majaczenia w ostrej fazie udaru na funkcjonowanie psychiczne pacjentów w trakcie hospitalizacji, po 3 i 12 miesiącach od udaru. Zbadano również częstość występowania zaburzeń emocjonalnych (depresji, lęku, apatii i agresji) u wszystkich pacjentów kolejno przyjmowanych na oddział udarowy i spełniających kryteria włączenia. Oceny funkcjonowania psychicznego dokonano w trakcie hospitalizacji, po 3 i 12 miesiącach od udaru. Do badania włączono grupę kolejnych 750 osób z rozpoznaniem udaru (niedokrwiennego/krwotocznego) lub TIA. Od 1 do 7 dnia pobytu w szpitalu pacjenci byli oceniani skalami przesiewowymi (Confusion Assessment Method/Confusion Assessment Method for the Intensive Care Unit) w celu identyfikacji majaczenia. Rozpoznanie delirium stawiano w oparciu o kryteria diagnostyczne DSM – V. W 7-10 dobie hospitalizacji dokonano pomiaru stanu emocjonalnego za pomocą skal: do pomiaru depresji –Kwestionariusz Zdrowia Pacjenta – 9 (PHQ – 9), do pomiaru lęku – Inwentarz Stanu i Cechy Lęku STAI, do pomiaru agresji – Skala Agresji Buss – Durkee (SABD), do pomiaru apatii – The Apathy Evaluation Scale w wersji dla klinicysty (AES – C). Po 3 i 12 miesiącach pacjenci zostali ponownie przebadani tymi samymi skalami do oceny stanu emocjonalnego, co w trakcie trwania hospitalizacji.

U 203 (27,07%) osób rozpoznano delirium. W trakcie hospitalizacji objawy depresyjne wystąpiły u 51,2% wszystkich włączonych do badania pacjentów (w tym u 47,14% osób bez majaczenia i u 72,6% pacjentów z majaczeniem). Po 3 miesiącach od udaru objawy depresyjne występowały u 56,18% osób (w tym u 53,4% pacjentów bez majaczenia i 73,91%, u których występowało delirium w trakcie hospitalizacji). Po 12 miesiącach objawy depresyjne utrzymywały

się u 52,14% badanych (w tym u 52,36% osób bez majaczenia i u 50% pacjentów z wcześniejszym majaczeniem).

Podczas hospitalizacji objawy lękowe wystąpiły u 29,03% wszystkich włączonych do badania pacjentów (w tym u 26,55% osób bez majaczenia i u 40,48% pacjentów z majaczeniem). Po 3 miesiącach od udaru objawy lękowe występowały u 26,96% osób (w tym u 23,13% pacjentów bez i 49,02% z delirium w trakcie hospitalizacji). Po 12 miesiącach objawy lękowe utrzymywały się u 16,89% badanych (w tym u 15,58 % osób bez i u 26,92% pacjentów z wcześniejszym majaczeniem).

Podczas hospitalizacji apatia wystąpiła u 31,35% wszystkich włączonych do badania pacjentów (w tym u 25,56% osób bez majaczenia i u 65,57% pacjentów z majaczeniem). Po 3 miesiącach od udaru apatia występowała u 34,72% osób (w tym u 30,27% pacjentów bez i 65,12% z majaczeniem w trakcie hospitalizacji). Po 12 miesiącach objawy apatii utrzymywały się u 24,68% badanych (w tym u 21,05 % osób bez majaczenia i u 59,09% pacjentów z wcześniejszym majaczeniem).

W trakcie hospitalizacji czynnik Agresja pojawił się u 8,62% osób, a Wrogość u 48,03% (w tym u 7,34% (Agresja) i 42,93% (Wrogość) osób bez majaczenia i u 15,07% (Agresja) i 75,34% (Wrogość) pacjentów z majaczeniem). Po 3 miesiącach od udaru czynnik Agresja pojawił się u 10,12% osób, a Wrogość u 21,39% (w tym u 9,76% (Agresja) i 19,53% (Wrogość) bez majaczenia i u 12,24% (Agresja) i 32,65% (Wrogość) pacjentów z majaczeniem). Po 12 miesiącach czynnik Agresja utrzymywał się u 7,25% osób, a Wrogość u 21,26% (w tym u 6,95% (Agresja) i 21,39% (Wrogość) osób bez majaczenia i u 10% (Agresja) i 20% (Wrogość) pacjentów ze zdiagnozowanym wcześniej majaczeniem).

Wyniki analiz wskazują, że majaczenie stanowi czynnik ryzyka depresji, lęku i wrogości w trakcie trwania hospitalizacji i 3 miesiące później oraz agresji i apatii w trakcie całego okresu trwania obserwacji. Majaczenie jest też

niezależnym czynnikiem ryzyka depresji i agresji podczas trwania hospitalizacji, lęku po 3 miesiącach oraz apatii podczas całego okresu trwania obserwacji. Wyniki badania pokazują, że zaburzenia emocjonalne są częstym następstwem udaru mózgu, a wystąpienie delirium stanowi dodatkowy czynnik ryzyka ich wystąpienia.

Celem drugiej pracy była ocena zmian w funkcjonowaniu (rozumianych jako poziom niepełnosprawności) oraz śmiertelności w ciągu roku od udaru u pacjentów, u których wystąpiły lub nie objawy depresyjne. Do badania włączono 524 pacjentów z diagnozą udaru lub TIA. Oceny występowania objawów depresyjnych dokonano między 7-10 dniem hospitalizacji za pomocą Kwestionariusza Zdrowia Pacjenta (PHQ – 9). Po 3 i 12 miesiącach od udaru zebrano dane na temat poziomu niepełnosprawności lub śmierci pacjenta. Do oceny stopnia niepełnosprawności użyto Zmodyfikowanej Skali Rankina (mRS).

W badanej grupie objawy depresyjne zdiagnozowano u 54,58% pacjentów w trakcie pobytu na oddziale. Osoby z depresją w porównaniu do tych bez objawów depresyjnych były istotnie starsze, częściej płci żeńskiej, rzadziej występował u nich udar lewopółkulowy i leczenie rekombinowanym tkankowym aktywatorem plazminogenu (rt – PA). U osób depresyjnych częściej występowało zapalenie płuc i miały wyższy poziom białka C-reaktywnego (CRP) w trakcie trwania hospitalizacji. Ponadto przed przyjęciem były znacznie bardziej niepełnosprawne fizycznie, częściej miały TIA lub udar w przeszłości i więcej chorób współistniejących. Wcześnie pojawiającym się objawom depresyjnym istotnie częściej towarzyszyły też inne stany neuropsychiatryczne tj. apatia, lęk, majaczenie i demencja.

Wyniki przeprowadzonych analiz wskazują, że pacjenci, u których wystąpiły objawy depresyjne w ostrej fazie udaru, mieli około sześciokrotnie większe ryzyko zgonu po trzech miesiącach od udaru i prawie 4,5-krotnie

większe ryzyko po 12 miesiącach, w porównaniu z pacjentami bez depresji. Depresja poudarowa negatywnie wpłynęła na poziom niepełnosprawności i śmiertelność po 3 i 12 miesiącach od udaru. Oba wyniki były niezależne od ciężkości udaru i współistniejących zaburzeń neuropsychiatrycznych.

Celem trzeciego badania była ocena związku pomiędzy poziomem białka C-reaktywnego (CRP) w krwi obwodowej a wystąpieniem objawów depresji poudarowej. Do badania włączono pacjentów, u których zdiagnozowano udar niedokrwienny lub TIA i oznaczono poziom CRP w surowicy w ciągu 48 godzin od wystąpienia objawów udaru. Pomiaru depresji dokonano za pomocą Kwestionariusza Zdrowia Pacjenta (PHQ – 9) u 405 pacjentów pomiędzy 7-10 dniem pobytu na oddziale oraz u 306 badanych 3 miesiące po udarze. W porównaniu do pacjentów z mniej nasilonymi objawami depresyjnymi, osoby z wyższą punktacją w PHQ – 9 (≥10) częściej były płci żeńskiej, cierpiały z powody nadciśnienia tętniczego, wcześniejszego udaru, obniżenia funkcji poznawczych przed udarem, przyjmowały leki przeciwdepresyjne przed wystąpieniem udaru i miały wyższy wynik w skali oceniającej występowanie współistniejących zaburzeń neuropsychiatrycznych (ocena Inwentarzem Neuropsychiatrycznym NPI). Poziom CRP był wyższy u osób z bardziej nasilonymi objawami depresyjnymi.

Wyniki analiz wskazują również, że poziom CRP powyżej 9,2 mg/L był związany z wyższym poziomem depresji w ostrej fazie udaru. Po 3 miesiącach od udaru w analizie jednoczynnikowej poziom CRP powyżej 4,3 mg / l wiązał się z większymi objawami depresyjnymi, natomiast związek ten tracił istotność w analizie wieloczynnikowej skorygowanej o nadciśnienie tętnicze, cukrzycę, majaczenie, stosowanie leków przeciwdepresyjnych i wynik w skali NPI. Uzyskane w badaniu wyniki wskazują, że wyższy poziom CRP jest związany z wczesnym wystąpieniem objawów depresyjnych w udarze niedokrwiennym.

VI. Summary

The aim of the first study was to evaluate the impact of delirium on mental functioning of patients during hospitalization, 3 and 12 months after the stroke. The frequency of emotional disorders (depression, anxiety, apathy and aggression) in all patients consecutively admitted to the stroke unit and meeting the inclusion criteria was also examined. Mental functioning was assessed during hospitalization, 3 and 12 months after the stroke. The study included a group of consecutive 750 patients diagnosed with stroke (ischemic or hemorrhagic) or transient ischemic attack (TIA). From day 1 to day 7 of hospital stay, patients were assessed using screening scales (Confusion Assessment Method / Confusion Assessment Method for the Intensive Care Unit) to identify delirium. The diagnosis of delirium was made on the basis of the DSM-V diagnostic criteria. On the 7-10th day of hospitalization, the emotional state was assesed using the following scales: for depression - Patient Health Questionnaire - 9 (PHQ - 9), for anxiety - State and Features Inventory STAI anxiety, for aggression - Buss - Durkee Aggression Scale (SABD), for apathy - The Apathy Evaluation Scale - version for the clinician (AES - C). After 3 and 12 months, the patients were re-examined with the same scales.

Delirium was diagnosed in 203 (27.07%) patients. During hospitalization, depressive symptoms occurred in 51.2% of all patients included in the study (in 47.14% of patients without delirium and in 72.6% of patients with delirium). Three months after the stroke, depressive symptoms were present in 56.18% of patients (in 53.4% of patients without delirium and in 73.91% of patients with delirium during hospitalization). After 12 months, symptoms

of depression were identyfied in 52.14% of the respondents (in 52.36% of those without delirium and in 50% of patients with delirium).

During hospitalization, anxiety symptoms occurred in 29.03% of all patients enrolled in the study (in 26.55% of those who were not diagnosed with delirium and in 40.48% of patients with delirium). Three months after the stroke, anxiety symptoms occurred in 26.96% of patients (in 23.13% of patients without delirium and in 49.02% of patients with delirium during hospitalization). After 12 months, anxiety symptoms persisted in 16.89% of the subjects (in 15.58% of those without delirium and in 26.92% of patients with delirium).

During hospitalization, apathy occurred in 31.35% of all patients enrolled in the study (in 25.56% of those with delirium and in 65.57% of patients with delirium). After 3 months, apathy was present in 34.72% of patients (in 30.27% of patients without delirium and in 65.12% of patients with delirium during hospitalization). After 12 months, symptoms of apathy were persistent in 24.68% of the subjects (in 21.05% of those without delirium and in 59.09% of patients with in-hospital delirium).

During hospitalization, the Aggression factor appeared in 8.62% of patients, and Hostility in 48.03% (including 7.34% (Aggression) and 42.93% (Hostility) of people who without delirium and in 15, 07% (Aggression) and 75.34% (Hostility) of patients with delirium). Three months after the stroke, Aggression appeared in 10.12% of people and Hostility in 21.39% (in 9.76% (Aggression) and in 19.53% (Hostility) of people without delirium and in 12.24% (Aggression) and in 32.65% (Hostility) of patients with delirium). After 12 months, the Aggression factor was present in 7.25% of the subjects, and Hostility in 21.26% (in 6.95% (Aggression) and 21.39% (Hostility) of those without delirium and in 10% (Aggression) and in 20% (Hostility) of patients previously diagnosed with delirium).

The results of the analyzes indicate that delirium is a risk factor for depression, anxiety and hostility during hospitalization and 3 months later,

as well as for aggression and apathy throughout the observation period. Delirium is also an independent risk factor for depression and aggression during hospitalization, anxiety after 3 months, and apathy during the entire follow-up period.

The results of the study show that emotional disorders are a common consequence of stroke, and the occurrence of delirium is an additional risk factor for their occurrence.

The aim of the second study was to assess changes in functioning (understood as the level of disability) and mortality within one year of stroke in patients with or without depressive symptoms. The study included 524 patients diagnosed with stroke or TIA. The occurrence of depressive symptoms was assessed between 7-10th day of hospitalization using the Patient Health Questionnaire (PHQ - 9). Three and 12 months after the stroke, data on the level of disability or death of the patient was collected. The Modified Rankin Scale (mRS) was used to assess the degree of disability.

In the study group, depressive symptoms were diagnosed in 54.58% of patients during hospitalization. Compared to those without depressive symptoms, people with depression were significantly older, more often females, less frequently had left-hemispheric stroke and received treatment with recombinant tissue plasminogen activator (rt - PA). Pneumonia was more common in depressed patients and they also had higher levels of C-reactive protein (CRP) during hospitalization. They also were significantly more physically disabled prior to hospitalization, less often had TIA or stroke in the past, and had more comorbidities. Early depressive symptoms were significantly more often accompanied by other neuropsychiatric disturbances such as apathy, anxiety, delirium and dementia.

The results of the analyzes indicate that patients who developed depressive symptoms in the acute phase of stroke had an approximately six-fold higher risk

of death three months after the stroke and almost 4.5-fold higher risk at 12 months, compared to patients without depression. Post-stroke depression negatively affected the level of disability and mortality 3 and 12 months after the stroke. Both outcomes were independent of the stroke severity and coexisting neuropsychiatric disorders.

The aim of the third study was to evaluate the relationship between the level of C-reactive protein (CRP) in the peripheral blood and the development of symptoms of post-stroke depression. The study enrolled patients who had been diagnosed with ischemic stroke or TIA and had CRP assessed within 48 hours of the stroke onset. Depression was measured using the Patient Health Questionnaire (PHQ - 9) in 405 patients between 7-10th day of hospitalization and in 306 patients 3 months after the stroke. Compared to patients with less severe depressive symptoms, those with higher PHQ-9 scores (≥10) were more often women; suffered from hypertension, previous stroke, and pre-stroke cognitive decline; took antidepressants before index stroke, and had higher score on the scale assessing the presence of comorbid neuropsychiatric disorders (assessment with the NPI Neuropsychiatric Inventory). CRP levels were higher in people with more severe depressive symptoms.

The results of the analyzes also indicate that CRP levels above 9.2 mg/l were associated with greater depression symptoms in the acute phase of stroke. Three months after the stroke CRP levels above 4.3 mg/l were associated with greater depressive symptoms in univariate analysis. This association was non-significant in the multivariate analysis adjusted for hypertension, diabetes mellitus, delirium, the use of antidepressant and the NPI score. The results obtained in the study indicate that a higher CRP level is associated with the early onset of depressive symptoms in ischemic stroke.

VII. Podsumowanie

Powyższy cykl publikacji wnosi następujące nowe informacje:

1. Zaburzenia emocjonalne są częstym następstwem udaru mózgu. Depresja poudarowa utrzymuje się u ponad połowy pacjentów aż do 12 miesięcy po udarze.
2. Majaczenie stanowi niezależny czynnik zwiększający ryzyko wystąpienia zaburzeń emocjonalnych po udarze.
3. Wystąpienie depresji poudarowej istotnie zwiększa ryzyko niepełnosprawności i śmierci po 3 i 12 miesiącach od udaru
4. Wyższy poziom białka C-reaktywnego (CRP) jest związany z wczesnym wystąpieniem objawów depresyjnych po udarze.

VIII. Piśmiennictwo

[1] Barker-Collo SL (2007) Depression and anxiety 3 months post stroke: prevalence and correlates. Archives of Clinical Neuropsychology 22, 519–31.
[2] Ayerbe L., Ayis S., Wolfe Ch., Rudd A. (2013) Natural history, predictors and outcomes of depression after stroke: systematic review and meta – analysis. The British Journal of Psychiatry 202, 14-2.
[3] Campbell Burton C.A., Murray J., Holmes J., Astin F., Greenwood D., Knapp P. (2013) Frequency of anxiety after stroke: a systematic review and meta – analysis of observational studies. International Journal of Stroke 8, 545-559
[4] Paradiso S, Robinson RG, Arndt S. (1996) Self-reported aggressive behavior in patients with stroke. Journal of Nervous and Mental Disease 184, 746–753.
[5] Kim JS, Choi S, Kwon SU, Seo YS.(2002) Inability to control anger or aggression after stroke. Neurology 58, 1106–1108.
[6] Yang S., Hua P., Shang X., Hu R., Mo X., Pan X. (2013) Predictors of early post ischemic stroke apathy and depression: a cross – sectional study. BMC Psychiatry 13, 164
[7] Chan K-L, Campayo A, Moser DJ, Arndt S, Robinson RG.(2006) Aggressive behavior in patients with stroke: association with psychopathology and results of antidepressant treatment on aggression. Archives of physical medicine and rehabilitation 87(6),793-798
[8] Kauhanen M, Korpelainen JT, Hiltunen P, Brusin E, Mononen H, Maatta R, et al.(1999) Poststroke depression correlates with cognitive impairment and neurological deficits. Stroke 30, 1875–80.
[9] Hosking, S., Marsh, N., & Friedman, P. (2000) Depression at 3-months poststroke in the elderly: Predictors and indicators of prevalence. Aging Neuropsychology & Cognition,7(4), 205–216.
[10] Nys GMS, van Zandvoort MJE, van der Worp HB, de Haan EHF, de Kort PLM, Kappelle LJ. (2005) Early depressive symptoms after stroke: neuropsychological correlates and lesion characteristics. Journal of Neurological Science 228, 27–33.
[11]. Wohleb, E. S., Franklin, T., Iwata, M. & Duman, R. S. (2016) Integrating neuroimmune systems in the neurobiology of depression. Nature Reviews Neuroscience 17, 497–511.

[12]. Miller, A. H. & Raison, C. L. (2016) The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature Reviews Immunology. 16, 22–34.
[13]. Krishnadas, R. & Cavanagh, J. (2012) Depression: an inflammatory illness? Journal of Neurology, Neurosurgery, and Psychiatry 83, 495–502.
[14]. Howren, M.B.; Lamkin, D.M.; Suls, J. (2009) Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. Psychosomatic Medicine 71, 171–186.
[15]. Haapakoski, R.; Mathieu, J.; Ebmeier, K.P.; Alenius, H.; Kivimaki, M. (2015) Cumulative meta-analysis of interleukins 6 and 1beta, tumour necrosis factor alpha and C-reactive protein in patients with major depressive disorder. Brain, Behavior, and Immunity 49, 206–215.
[16]. Gimeno, D.; Kivimaki, M.; Brunner, E.J.; Elovainio, M.; De Vogli, R.; Steptoe, A.; Kumari, M.; Lowe, G.D.O.; Rumley, A.; Marmot, M.G.; et al. (2009) Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychological Medicine 39, 413–423.
[17]. Strawbridge, R.; Arnone, D.; Danese, A.; Papadopoulos, A.; Herane Vives, A.; Cleare, A.J.(2015) Inflammation and clinical response to treatment in depression: A meta-analysis. European Neuropsychopharmacology 25, 1532–1543.
[18] Schultz, S. K., Castillo, C. S., Kosier, J. T., & Robinson, R. G. (1997). Generalized anxiety and depression: Assessment over 2 years after stroke. American Journal of Geriatric Psychiatry, 5(3), 229–237.
[19] Castillo, C. S., Schultz, S. K., & Robinson, R. (1995). Clinical correlates of early-onset and late-onset poststroke generalised anxiety. American Journal of Psychiatry, 152(8), 1174–1181.
[20] Castillo, C. S., Starkstein, S. E., Fedoroff, J. P., & Price, T. R. (1993). Generalized anxiety disorder after stroke. Journal of Nervous & Mental Disease, 181(2), 100–106.
[21] Cummings JL, Bogousslavsky J. Emotional consequences of focal brain lesions: an overview. In: Bogousslavsky J,Cummings JL, eds. Behavior and Mood Disorders in Focal Brain Lesions. Cambridge University Press, Cambridge, 2000, 1–20.
[22] Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. (2005) Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke – the Sydney Stroke Study. Psychological Medicine, 35, 1707–1716.
[23] Hama S., Yamashita H., Yamawaki S i Kurisu K. (2011) Post – stroke depression and apathy: Interactions between functional recovery, lesion location and emotional response. Psychogeriatrics, (11): 68-76

[24]. Gustafson, Y.; Olsson, T.; Eriksson, S.; Asplund, K.; Bucht, G. (1991) Acute confusional states (delirium) in stroke patients. Cerebrovascular Diseases, 1, 257–264.
[25]. Shi, Q.; Presutti, R.; Selchen, D.; Saposnik, G. (2012) Delirium in acute stroke: A systematic review and meta-analysis. Stroke, 43, 645–649.
[26]. Pasinska,P.; Wilk,A.; Kowalska, K.; Szyper-Maciejowska, A.; Klimkowicz-Mrowiec, A. (2019) The long-term prognosis of patients with delirium in the acute phase of stroke: PRospective Observational POLIsh Study (PROPOLIS). Journal of Neurology, 266, 2710–2717
[27]. Mansutti, I.; Saiani, L.; Palese, A. (2019) Delirium in patients with ischaemic and haemorrhagic stroke: Findings from a scoping review. European Journal of Cardiovascular Nursing, 18, 435–448.
[28]. Davydow, D.S. (2009) Symptoms of depression and anxiety after delirium. Psychosomatics, 50, 309–316.

IX. Oświadczenia współautorów

Kraków, dn. 02.02.2021

lek. Jakub Droś
(tytuł, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „ Delirium Post-Stroke: Short- and Long-Term Effect on Depression, Anxiety, Apathy and Aggression (Research Study-Part of PROPOLIS Study)" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to analiza i opracowanie wyników badania oraz przygotowanie manuskryptu publikacji.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez mgr Katarzynę Kowalską, jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część w/w pracy wykazuje indywidualny wkład mgr Katarzyny Kowalskiej przy opracowaniu metodologii badania, zbieraniu danych do badania i przygotowaniu manuskryptu publikacji.

lek. Jakub Droś
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Małgorzata Mazurek

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OŚWIADCZENIE

Jako współautor pracy pt. „ Delirium Post-Stroke: Short- and Long-Term Effect on Depression, Anxiety, Apathy and Aggression (Research Study-Part of PROPOLIS Study)" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to zbieranie danych i przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez mgr Katarzynę Kowalską, jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część w/w pracy wykazuje indywidualny wkład mgr Katarzyny Kowalskiej przy opracowaniu metodologii badania, zbieraniu danych do badania i przygotowaniu manuskryptu publikacji.

Małgorzata Mazurek

Kraków, dn. 02. 02. 2021

dr Paulina Pasińska

(tytuł, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „ Delirium Post-Stroke: Short- and Long-Term Effect on Depression, Anxiety, Apathy and Aggression (Research Study-Part of PROPOLIS Study)" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to opracowanie metodologii badania i zbieranie danych.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez mgr Katarzynę Kowalską, jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część w/w pracy wykazuje indywidualny wkład mgr Katarzyny Kowalskiej przy opracowaniu metodologii badania, zbieraniu danych do badania i przygotowaniu manuskryptu publikacji.

Paulina Pasińska

Katowice, dn. 25.01.2021r.

Dr hab.n.med. Agnieszka Gorzkowska

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(tytuł, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „ Delirium Post-Stroke: Short- and Long-Term Effect on Depression, Anxiety, Apathy and Aggression (Research Study-Part of PROPOLIS Study)" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to nadzór nad badaniem i przygotowanie manuskryptu publikacji.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez mgr Katarzynę Kowalską, jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część w/w pracy wykazuje indywidualny wkład mgr Katarzyny Kowalskiej przy opracowaniu metodologii badania, zbieraniu danych do badania i przygotowaniu manuskryptu publikacji.

Z poważaniem,

Agnieszka Gorzkowska

Kraków, dn. 02.02.2021

Dr hab. n. med. Aleksandra Klimkowicz-Mrowiec

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OŚWIADCZENIE

Jako współautor pracy pt. „ Delirium Post-Stroke: Short- and Long-Term Effect on Depression, Anxiety, Apathy and Aggression (Research Study-Part of PROPOLIS Study)" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to opracowanie koncepcji badania i metodologii, opracowanie wyników badania, przygotowanie manuskryptu publikacji oraz nadzór nad prowadzonym badaniem.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez mgr Katarzynę Kowalską, jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część w/w pracy wykazuje indywidualny wkład mgr Katarzyny Kowalskiej przy opracowaniu metodologii badania, zbieraniu danych do badania i przygotowaniu manuskryptu publikacji.

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Kraków, dn. 03.02.2021

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OŚWIADCZENIE

Jako współautor pracy pt. „Early Depression Independently of Other Neuropsychiatric Conditions, Influences Disability and Mortality after Stroke (Research Study-Part of PROPOLIS Study)" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to analiza i opracowanie wyników badania i korekta merytoryczna manuskryptu publikacji.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez mgr Katarzynę Kowalską, jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część w/w pracy wykazuje indywidualny wkład mgr Katarzyny Kowalskiej przy opracowaniu koncepcji i metodologii badania, zbieraniu danych do badania i przygotowaniu manuskryptu publikacji.

Pełnomocnik
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Kraków, dn. 02.02.2021

Dr hab. n. med. Aleksandra Klimkowicz-Mrowiec
.....

(tytuł, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Early Depression Independently of Other Neuropsychiatric Conditions, Influences Disability and Mortality after Stroke (Research Study-Part of PROPOLIS Study)" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to opracowanie koncepcji badania i metodologii, opracowanie wyników badania, przygotowanie manuskryptu publikacji oraz nadzór nad prowadzonym badaniem.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez mgr Katarzynę Kowalską, jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część w/w pracy wykazuje indywidualny wkład mgr Katarzyny Kowalskiej przy opracowaniu koncepcji i metodologii badania, zbieraniu danych do badania i przygotowaniu manuskryptu publikacji.

Dr hab. n. med. Aleksandra Klimkowicz-Mrowiec
specjalista neurolog
3398184

Kraków, dn. 03.02.2021

lek. Aleksander Wilk

(tytuł, imię i nazwisko)

OŚWIADCZENIE

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Aleksander W.Wc

Kraków, dn. 02.02.2021

dr Paulina Paniśka

(tytuł, imię i nazwisko)

OŚWIADCZENIE

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Paulina Paniśka

Kraków, dn. 02.02.2021

lek. Jakub Dros
(tytuł, imię i nazwisko)

OŚWIADCZENIE

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lek. Jakub Dros
3652732

Kraków, dn. 03.02.2021

Prof. dr hab. med. Agnieszka Słowik

(tytuł, imię i nazwisko)

OŚWIADCZENIE

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KIEROWNIK
Katedry i Kliniki Neurologii UJ CM
prof. dr hab. med. Agnieszka Słowik

Kraków, dn. 20.01.21

DR ELŻBIETA KLIMIEC-MOSKAL

(tytuł, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „C-reactive protein and post-stroke depressive symptoms" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to zbieranie danych.

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Elżbieta Klimiec-Moskal

Kraków, dn. 02.02.2021

dr Paulina Pasińska

(tytuł, imię i nazwisko)

OŚWIADCZENIE

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Paulina Pasińska

Kraków, dn. 03.02.2021

PROF. DR HAB. MED. Joanna Pera
(tytuł, imię i nazwisko)

OŚWIADCZENIE

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Kraków, dn. 03.02.2021

Prof. dr hab. med. Tomasz Dziedzic

(tytuł, imię i nazwisko)

OŚWIADCZENIE

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T. Dziedzic

Kraków, dn. 02.02.2021

Dr hab. n. med. Aleksandra Klimkowicz-Mrowiec
.....

(tytuł, imię i nazwisko)

OŚWIADCZENIE

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