INTRODUCTION

Spontaneous intracerebral hemorrhage (sICH) today represents an important social and economic burden worldwide due to its high morbidity, mortality, and disability rates (Dastur, Yu, 2017). sICH occurs predominantly in patients older than 50 years and is usually caused by the rupture of small deep penetrating blood vessels of the brain as a result of prolonged and uncontrolled hypertension (HTA) (Jolink et al., 2015). Pharmacotherapy of this serious disorder poses a great challenge for clinicians given the complexity of its clinical features and the possible occurrence of numerous complications during hospitalization. It usually involves the simultaneous use of multiple medicines for: (i) reducing high blood pressure and/or intracranial pressure, (ii) correction of hemorrhagic abnormalities, if any, (iii) preventing or treating seizures, (iv) reducing fever, (v) treating hyperglycemia, (vi) prevention of deep vein thrombosis (DVT)/pulmonary embolism (PE), (vii)
prophylaxis or treatment of infection, etc. (Dastur, Yu, 2017; Hemphill et al., 2015; Küppers-Tiedt, Steiner, 2015). Such polypharmacy increases the likelihood of serious drug interactions, exposing the sICH patients to the additional risk of poor health and economic outcomes (Rosas-Carrasco et al., 2011).

Potential drug-drug interactions (pDDIs) refer to possible changes in the efficacy and/or safety of one or both drugs in combination if used simultaneously. According to the severity, pDDIs were classified as contraindicated (life-threatening combinations to be avoided), major (interactions requiring intensive clinical monitoring as they may be life-threatening), moderate (those that may result in worsening of the patient’s condition), and minor (with limited clinical effects) (Hasan et al., 2012). The use of interaction checkers, i.e. online software operating on the principle of regular updating of databases is the most effective modern way to identify pDDIs. Due to good practical performance, the ones that are commonly used include Lexi-Interact, Micromedex®, Medscape and Epocrates (Kheshti, Aalipour, Namazi, 2016).

According to the previous studies, the prevalence of pDDIs among stroke patients ranges from 61 to almost 100% (Venkateswaramurthy et al., 2016; Caratozzolo, Gipponi, Marengoni, 2016). The number of prescribed medications (Venkateswaramurthy et al., 2016; Caratozzolo, Gipponi, Marengoni, 2016; Aleksic et al., 2019) and the use of antipsychotics were identified as the relevant predictors of pDDI in stroke patients (Aleksic et al., 2019). However, these studies enrolled vast majority of patients with acute ischemic stroke (AIS), so no reports of possible drug interactions in patients with separate hemorrhagic stroke have been published so far. Given the practical relevance of pDDIs in patients with severe illness such as sICH, the aim of this study was to determine the frequency of pDDI and the types of drugs involved in the most important pDDIs, as well as to identify significant factors associated with the occurrence of contraindicated pDDIs (pCDDI) in hospitalized patients with sICH.

MATERIAL AND METHODS

The research was designed as a retrospective cross-sectional study among consecutive patients with sICH who did not require neurosurgical intervention and were treated at the neurological intensive care unit (NICU), the Clinical Center Kragujevac (CCK), Serbia during the three-year period (2012-2014). The CCK is the medical center located in Kragujevac, Serbia. It is one of four medical centres in Serbia and serves more than 2 million people mostly from central and western Serbia. It contains 37 organizational units, of which 15 are clinics, 7 centers and 15 service units. The Neurological Clinic of the CCK has five departments: the neurological intensive care unit, polyclinic diagnostic department, department of demyelinating diseases, department of neurodegenerative diseases and department of neurophysiology. The research was approved by the Ethics Committee of the CCK (No. 01/8745).

All necessary data were collected from the patients’ medical files. The inclusion criteria encompassed patients aged 18 years and over, those diagnosed with ICH (ICD-10 code I61.0-I61.9) and those prescribed at least two drugs during hospitalization. On the other hand, patients whose hospitalization in NICU lasted less than 7 days, those who were diagnosed with other neurological diseases (i.e. degenerative, inflammatory, autoimmune, malignant, etc.) and patients with incomplete medical files were excluded from the study. Drugs were prescribed on electronic prescriptions mainly by neurology specialists, but also by specialists in clinical pharmacology, internal medicine, nephrology and other fields of medicine, who prescribed medications as part of consultative examinations. The electronic prescribing system in the CCK does not provide clinical decision support alerts to warn of potential DDIs.

For each day of hospitalization, the online checker Micromedex® software (Truven Health Analytics LLC, 2020) was used to detect pDDIs. If a particular drug was not covered by the Micromedex database, its interactions were not considered. The Micromedex® classified pDDIs according to severity (contraindicated, major, moderate and minor) and scientific evidence (excellent, good, fair). According to the Micromedex, if pDDIs belong to the category of contraindicated (pCDDI), that means the drugs are contraindicated for concurrent use. Major pDDIs may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects. The occurrence of
moderate pDDIs increases the risk of exacerbation of patient’s condition to a certain extent and usually requires changes of pharmacotherapy. Minor pDDIs are of the least clinical significance and usually do not require changes of therapy. Excellent scientific evidence refers to pDDIs whose occurrence has been proven in controlled clinical studies. Good scientific evidence means that the documentation strongly suggests the interaction exists, but well-controlled studies are lacking. Finally, for pDDIs with fair scientific evidence, the available documentation is poor, but pharmacologic considerations lead clinicians to suspect the interaction exists, or the documentation is good for a pharmacologically similar drug. The main outcomes of interest were the exposure to pDDI/pCDDI.

Two clinical pharmacologists, SJ and SS, independently reviewed and agreed with the classification of pDDIs according to severity and evidence.

Based on the presence or absence of pCDDI, all participants were separated into two groups. Differences between the groups were then examined for the prevalence of prior exposure to the assumed factors associated with the outcome mentioned above.

The numerous factors were analyzed for their contribution to pCDDI: demographic characteristics of patients (gender, age in years), characteristics of the hospitalization (transfer from another ward, length of hospitalization), clinical features of patients [total number and types of comorbidities (HTA, cardiomyopathy, diabetes mellitus type 2, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, anemia, liver cirrhosis), Charlson comorbidity Index (Goldstein et al., 2004), complications during the hospitalization including specific complications of ICH (delirium, seizures, coma, pneumonia, disturbances of glucose level during the hospitalization, acute kidney injury), fever (defined as at least one episode of elevated body temperature above 38°C during the hospital stay), and serum laboratory values]. Also, we analyzed the characteristics of prescribed pharmacotherapy [the total number of drugs, polypharmacy (i.e. use of 5 and more drugs daily), total number of medications from different anatomical/therapeutic/chemical (ATC) groups (WHO, 2020), certain groups of drugs that are likely to be involved in clinically relevant interactions and are commonly prescribed to these patients to prevent or treat complications of sICH (antibiotics, antipsychotics, antidepressants, anticoagulant therapy (low-molecular-weight heparins (LMWH) with or without oral anticoagulant therapy), dual antiplatelet therapy and statins)], as well as the data indicating the severity and scientific evidence of pDDIs other than pCDDIs.

The continuous data were summarized as medians, interquartile ranges (IQRs) and minimum and maximum values, while categorical variables were presented as frequencies and percentages. Chi-square test ($\chi^2$) was used for comparisons of categorical variables, and Fisher’s exact test analyzed the difference in proportions of two nominal variables with small frequencies of some categories Student’s T-test or Mann-Whitney U test was used for examining the differences between continuous variables. The connection between the total number of pDDIs and certain continuous variables was ascertained using the Spearman’s correlation coefficient. The influence of confounding and independent variables on the occurrence of dichotomous outcome (i.e. pCDDI) was calculated using the logistic regression model with backward stepwise selection of predictors. The strength of association is expressed by crude and adjusted odds ratio (OR) with 95% confidence interval (95% CI). The significant association was assumed if 95% CI did not include the value of 1. The p<0.05 was considered a statistically significant value for all analyses. The IBM SPSS Inc, Chicago IL, version 18, was used to perform all statistical analyses.

RESULTS

This study enrolled a total of 110 subjects diagnosed with sICH, 65 (59.1%) men and 45 (40.9%) women. The median age of the entire patient sample was 69.00 (IQR 60 – 78; 37 - 89), and men (64.0; IQR 58 - 77) were significantly younger than women (73.0; IQR 65 - 79.75) ($\chi^2 = 978.000, p = 0.01$). There was 57.9% of patients aged 65 years and over. The fatal outcome was observed in 35 patients (31.8%). The median length of hospitalization in NICU was close to three weeks (Table I), and median number of prescribed drugs was slightly more than 16 (16.50, IQR 13-19.25).
### TABLE I - Clinical characteristics of patients with sICH

| VARIABLES | VALUES |
|------------|--------|
| Durability of hospitalization in NICU\(^2\) in days (median, IQR, range (min-max)) | 18.00; 13-25; 7-41 |
| Number of comorbidities (median, IQR, range (min-max)) | 4.00; 3-5, 2-9 |
| Hypertension (n (%)) of patients | 96 (87.3) |
| Fever (n (%)) of patients | 46 (41.8) |
| Disturbances of glucose level during hospitalization without DM2\(^1\) (n (%)) of patients | 35 (31.8) |
| Acute kidney injury during hospitalization (n(%)) of patients | 34 (30.9) |
| Cardiomyopathy (n(%) of patients) | 31 (28.2) |
| DM2 (n(%) of patients) | 26 (23.6) |
| Atrial fibrillation (n(%) of patients) | 14 (12.7) |
| Delirium (n(%) of patients) | 12 (10.9) |
| Epilepsy (n(%) of patients) | 11 (9.9) |
| Pneumonia (n(%) of patients) | 8 (7.3) |
| Chronic kidney disease (n(%) of patients) | 6 (5.5) |
| Recurrent stroke (n(%) of patients) | 6 (5.5) |
| Coma (n(%) of patients) | 5 (4.5) |
| Chronic obstructive pulmonary disease (n(%) of patients) | 5 (4.5) |
| Anemia (n(%) of patients) | 3 (2.7) |
| Dementia (n(%) of patients) | 1 (0.9) |
| Liver cirrhosis (n(%) of patients) | 0 |
| Transfer from another ward (n(%) of patients) | 0 |
| Glomerular filtration rate (ml/min/1.72m\(^2\)) (median, IQR, range (min-max)) | 69.00; 14-89; 7-170 |

\(^1\)interquartile range \(^2\)Neurological Intensive Care Unit

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A total of 258 different pDDIs were detected in 108 (98.2%) patients. In addition, a total of 1016 pDDIs exposures were observed during the hospitalization in all patients. The median number of pDDIs was 8.00 (IQR 4.75 - 13.00; 1 - 30). The same patient could be exposed to different pDDIs by severity: pCDDIs were recorded in 20% of patients, major in 90.0%, moderate in 90.0% and minor pDDIs in 35.5%. A significant positive and strong (for some variables) correlation was observed between the total number of pDDIs and: the number of comorbidities (p<0.01, r=0.314), length of hospitalization (p<0.01, r=0.312), number of prescribed medications (p<0.01, r=0.740) and number of different pharmacological-therapeutic subgroups of drugs according to ATC classification (p<0.01, r=0.731).

The highest percentage of detected pDDIs according to severity was major (126/48.8%), followed by moderate (120/46.5%). Enoxaparin participated in major pDDIs with diclofenac (1.8%), warfarin (0.9%) and ketorolac (1.8%). A total of 10 moderate or major pDDIs with warfarin were recorded (8 in only one patient), while two participants had warfarin-ranitidine and warfarin-ketorolac interactions, classified as moderate and major pDDIs, respectively.

As previously mentioned, 5 different pCDDIs were observed in one-fifth of the total number of participants (i.e. in 22 of them), and with the exception of one patient with two recorded pCDDIs, all others were exposed to only one pCDDI. Most pDDIs were with fair (109/41.3%), or with good scientific evidence (107/41.5%). Ceftriaxone-
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calcium salts, metoclopramide-risperidone, ketorol-ac
diclofenac were the most commonly identified pCDDIs,
while diclofenac-furosemide, fosinopril-potassium
chloride and enalapril-potassium chloride were the pairs
drugs most commonly involved in major pDDIs.

No significant difference in mortality was found
between the compared groups of patients with (27.3%)
and without (33.0%) pCDDI ($\chi^2 = 0.262, p = 0.659$).
The differences between them with respect to putative
risk factors are presented in Table IIA. The duration of
hospitalization was longer and the number of patients
with dementia was higher among participants in whom
pCDDI was observed. Also, in this group, the number
of prescribed drugs and the number of pharmacological-
therapeutic subgroups of drugs were higher, while
anticoagulant therapy and dual antiplatelet therapy
were more frequently prescribed. All aforementioned
differences reached the statistical significance. The
frequencies of all other potential predictors did not
significantly differ between the two compared groups
(Table IIA). Also, there was no statistically significant
difference between these two groups in terms of the
number of pDDIs with respect to other levels of severity
of pDDIs (major, moderate, minor), or with the degree
of scientific evidence of pDDIs (excellent, good, fair).

Univariate logistic regression showed that potentially
significant factors associated with pCDDI in patients
with sICH were the length of hospitalization, number of
prescribed drugs, number of pharmacological-therapeutic
subgroups of drugs according to ATC classification, and
prescription of anticoagulant therapy (LMWH plus/minus
warfarin). After the adjustment by means of logistic
regression in the final multivariate logistic regression model
with acceptable characteristics (Cox and Snell R square
0.151, Nagelkerke R square 0.239, Hosmer-Lemeshow
Chi-square 11.523, df = 8, p = 0.740, and overall accuracy
of 82.7%), only two factors that increase the likelihood
of pCDDI were identified: prescribing of multiple drugs
from various pharmacological-therapeutic subgroups
(with minor influence on the observed outcome) and use
of anticoagulant therapy (chance of the observed outcome
increased slightly more than sevenfold) (Table IIB).

### Table IIA - Baseline demographic and clinical characteristics of two compared groups of patients

| Demographic and clinical characteristics | Patients with pCDDI n=22 | Patients without pCDDI n=88 | Test value and p | Crude OR$^1$ with 95% CI$^2$ |
|------------------------------------------|--------------------------|----------------------------|-----------------|------------------|
| Gender                                   | Male 17 (77.3) Female 5 (22.7) | Male 48 (54.5) Female 40 (45.5) | $\chi^2=3.761 p=0.052$ | 0.35 (0.12-1.04) |
| Age(years)Median(IQR$^3$)                | 66.5 (57-78.25)          | 69.00 (60.5-78.5)          | U=851.000 Z=-0.648 p=0.517 | 0.99 (0.95-1.03) |
| Number of diagnosis Median (IQR)         | 4.00 (3-5.25)            | 4.00 (3-5)                 | U=876.000 Z=-0.703 p=0.482 | 1.11 (0.83-1.48) |
| Length of hospitalization Median (IQR)   | 24.00 (12-27)            | 18.00 (13-23)              | U=762.000 Z=-1.541 p=0.123 | 1.07 (1.00-1.14) |
| Recurrent stroke$^a$                     | 1 (4.5)                  | 5 (5.7)                   | $\chi^2=0.000 p=0.834$ | 0.79 (0.09-7.13) |
| Hypertension                             | 19 (86.4)                | 77 (87.5)                 | $\chi^2=0.000 p=0.886$ | 0.90 (0.23-3.57) |
| Cardiomyopathy                           | 8 (36.4)                 | 23 (26.1)                 | $\chi^2=0.474 p=0.340$ | 1.61 (0.60-4.35) |
| Atrial fibrillation$^a$                   | 3 (13.6)                 | 11 (12.5)                 | $\chi^2=0.000 p=0.886$ | 1.10 (0.28-4.36) |
| Diabetes mellitus type 2                 | 6 (27.3)                 | 20 (22.7)                 | $\chi^2=0.028 p=0.654$ | 1.27 (0.44-3.69) |
| Anemia$^a$                                | 1 (4.5)                  | 2 (2.3)                   | $\chi^2=0.000 p=0.558$ | 2.04 (0.18-23.67) |
### TABLE IIA - Baseline demographic and clinical characteristics of two compared groups of patients

| Demographic and clinical characteristics | Patients with pCDDI n=22 | Patients without pCDDI n=88 | Test value and p | Crude OR with 95% CI |
|------------------------------------------|--------------------------|----------------------------|------------------|---------------------|
| Dementia†                                | 1 (4.5)                  | 0                          | χ²=0.568 p=0.045* | N/A                 |
| Disturbances of glucose level without diabetes mellitus type2 | 7 (47.1)                 | 32 (43.8)                 | χ²=0.000 p=0.811  | 0.87 (0.29-2.62)    |
| Chronic kidney disease (CKD)§          | 1 (4.5)                  | 5 (5.7)                   | χ²=0.000 p=0.834  | 0.79 (0.09-7.13)    |
| Acute kidney injury without CKD         | 9 (42.9)                 | 25 (31.2)                 | χ²=0.551 p=0.316  | 1.65 (0.62-4.42)    |
| Glomerular filtration rate (ml/min/1.72m²) | 66.50 (48.75-96.5)       | 69.00 (48.5-88.5)         | U=928.500 Z=-0.050 p=0.960 | 1.01 (0.98-1.02)    |
| Pneumonia§                              | 3 (13.6)                 | 5 (5.7)                   | χ²=0.682 p=0.199  | 2.62 (0.58-11.93)   |
| Epilepsy§                               | 2 (9.1)                  | 9 (10.2)                  | χ²=0.000 p=0.874  | 0.88 (0.18-4.39)    |
| Delirium§                               | 3 (13.6)                 | 9 (10.2)                  | χ²=0.006 p=0.646  | 1.39 (0.34-5.62)    |
| Chronic obstructive pulmonary disease§  | 2 (9.1)                  | 3 (3.4)                   | χ²=0.327 p=0.252  | 2.83 (0.44-18.00)   |
| Coma§                                   | 2 (9.1)                  | 3 (3.4)                   | χ²=0.327 p=0.252  | 2.83 (0.44-18.00)   |
| Fever                                   | 12 (54.5)                | 34 (38.6)                 | χ²=1.235 p=0.176  | 1.91 (0.74-4.89)    |
| Charlson comorbiditiy index with adjustment of age Median (IQR) | 5.00 (IQR: 4-6)          | 5.00 (4-6)                | U=914.000 Z=-0.409 p=0.682 | 0.94 (0.75-1.18)    |
| Charlson comorbiditiy index without adjustment of age Median (IQR) | 2.50 (1-4)               | 3.00 (1-3.75)             | U=936.500 Z=-0.242 p=0.809 | 1.05 (0.80-1.38)    |
| Antibiotics                             | 20 (90.9)                | 76 (86.4)                 | χ²=0.046 p=0.567  | 1.58 (0.33-7.63)    |
| Antipsychotics                          | 7 (31.8)                 | 14 (15.9)                 | χ²=1.946 p=0.089  | 2.47 (0.85-7.14)    |
| Antidepressants§                         | 0                       | 2 (2.3)                   | χ²=0.000 p=0.475  | N/A                 |
| HMG-CoA3 reductase inhibitors (statins) | 0                       | 17 (19.3)                 | χ²=3.657 p=0.025* | N/A                 |
| Anticoagulant therapy                   | 5 (22.7)                 | 2 (2.3)                   | χ²=9.163 p=0.000* | 12.65 (2.26-70.65)  |
| Dual antiplatelet therapy§              | 2 (9.1)                  | 1 (1.1)                   | χ²=1.735 p=0.040* | 8.70 (0.75-100.73)  |
| Numbers of drugs prescribed             | Median: 19.50 IQR: 16.75; 23 | Median: 16 IQR: 13; 19 | U=523.500 Z=-3.331p=0.001* | 1.21 (1.80-1.36)    |
| The number of anatomical therapeutic (ATC) group of drugs | Median: 19.00 IQR: 15; 22.25 | Median:15.00 IQR:12.25; 18.00 | U=534.500 Z=-3.251p=0.001* | 1.23 (1.09-1.40)    |
| Polypharmacy                            | 5-8 drugs: 0 (0) ≥9 drugs: 22 (100) | 5-8 drugs: 3 (3.4) ≥9 drugs: 85 (96.6) | χ²=0.771 p=0.380 | N/A                 |

*the number of patients was <5 in at least one group (Fisher’s exact test was used)/Odd ratio 3Confidence interval 4interquartile range

1 Odds ratio 2 Confidence interval 3 interquartile range 4 not applicable * statistically significant value
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### TABLE IIB - Predictors of pCDDIs

| Predictor                                      | Crude OR with 95% CI | Adjusted OR with 95% CI |
|------------------------------------------------|----------------------|-------------------------|
| Length of hospitalization                      | 1.07 (1.00-1.14)     | 1.03 (0.96-1.11)        |
| Number of prescribed drugs                    | 1.21 (1.08-1.36)     | 0.97 (0.53-1.79)        |
| The number of anatomical therapeutic (ATC) group of drugs | 1.23 (1.09-1.40)     | 1.19 (1.05-1.35) #      |
| Anticoagulant therapy                          | 12.65 (2.26-70.65)   | 7.40 (1.13-48.96) #     |

- Adjusted for the age and sex, average number of diagnosis per patient, Charlson comorbidity index with and without adjustment of age, use of antibiotics, antipsychotics, antidepressants, statins, and polypharmacy (these variables are not shown for the sake of clarity)
- *observed in the final model of logistic regression
- Odds ratio °Confidence interval
- # Significant association

### DISCUSSION

One of the most important findings of this study relates to the widespread occurrence of pDDI in sICH patients treated in NICU of almost 100%, regardless of their severity. Cardiovascular drugs were the most commonly involved medicines in pDDIs. A relevant number of participants (one-fifth of total) were exposed to at least one pCDDI. The use of multiple drugs from different pharmacological-therapeutic subgroups and the prescribing of anticoagulant therapy were observed as major, potentially modifiable factors associated with pCDDI.

At the Department of General Neurology at the CCK, Kostic et al. found a high prevalence of 59% of contraindicated and major pDDIs according to the Micromedex® (Kostic, Zivkovic-Zaric, Jankovic, 2019), which is to some extent consistent with our findings. According to the literature data, the prevalence of pDDIs in the intensive care units (ICU) ranges from 46.3-96.5% (Zheng et al., 2018; Shakeel et al., 2018).

In a previous study investigating pDDIs in patients with AIS, we showed that all patients were exposed to at least one pDDI (Aleksic et al., 2019). Besides, the study encompassed patients with AIS and sICH (only 4% of patients were diagnosed with sICH) discovered at least one pDDI in 89% during the hospitalization (Venkateswaramurthy et al., 2016). Finally, another small study showed that 24/37 (65%) of patients with sICH had at least one severe (contraindicated and/or major) pDDIs according to the INTERCheck software (Caratozzolo, Gipponi, Marengoni, 2016). The high prevalence of pDDI/pCDDIs, reflecting the potentially inappropriate drug therapy to which our patients were subjected, could be explained by the following: (i) predominantly elderly, multimorbid, and functionally incapacitated patients with serious illness, such as sICH, required fairly long treatment at the NICU, mainly using multiple medications administered parenterally; (ii) many of these drugs are characterized by a narrow therapeutic index and exhibit highly variable pharmacokinetics in such severe patients, resulting in pCDDI when combined; (iii) moreover, we believe that the major polypharmacy observed in our sample is largely due to the prescribing behavior of many different consultant physicians who were particularly prone to treat symptoms in our patients; (iv) also, we identified pDDIs/pCDDIs at each hospitalization day for all prescribed medications, not just at the admission or discharge from the hospital as shown in prior researches (Caratozzolo, Gipponi, Marengoni, 2016; Castilho et al., 2018; Busa et al., 2018).

Older people (nearly 60% of our sample), as the largest consumers of drugs usually due to multiple comorbidities requiring polypharmacy, are at particular risk of interactions. This is supported by the study in hospitalized patients over 60 years of age (Murtaza et al., 2016). The most common chronic disease in our patients was hypertension, which in addition to heart disease and chronic kidney disease, proved to be a predictor of pDDIs (Shakeel et al., 2018; Subramanian, Adhimoolam, Kannan, 2018; Adane, Maxwell, Kosisochi, 2017; Okoro, Farate, 2019). However, as expected, almost 90% of all our patients (from both compared groups) suffered from hypertension and received antihypertensive drugs, so it is not surprising that the association between hypertension...
and the occurrence of pCDDI did not reach a significance level.

Certain groups of drugs are more likely to participate in pDDIs. We observed the antibiotic use in approximately 90% of patients, and these drugs account for up to 26.4% of all pDDIs as shown previously (Biradar et al., 2016; Kuscu et al., 2018). The most common pCDDI in the present study was ceftriaxone-calcium salts, indicating the lack of awareness among clinicians of possible intravascular deposition of ceftriaxone-calcium complex that could potentially lead to embolism (Bradley et al., 2009; Steadman et al., 2010). The vast majority of clinically relevant drug-drug interactions observed in our study contained NSAIDs. NSAIDs are widely used medicines for the symptomatic treatment of fever, pain and inflammation. There are controversial reports on the use of these drugs and the risk of stroke (Lapi et al., 2016; Chang et al., 2010; Ungprasert, Matteson, Thongprayoon, 2016). However, the involvement of NSAIDs in serious DDIs is known to be associated with a higher incidence of serious gastrointestinal, renal and cardiovascular adverse events, which may expose patients to the risk of additional comorbidities (Moore, Pollack, Butkerait, 2015). Moreover, we rarely observed inappropriate exposure to pCDDIs involving ketorolac (as the most potent analgesic and at the same time, the least safe drug in the group of NSAIDs) paired with aspirin and diclofenac.

A prolonged hospital stay accompanied with longer drug therapy using plenty of medicines, usually shows a significant correlation with the total number of pDDIs (Sharma, Chhetri, Alam, 2014; Rodrigues et al., 2017). Moreover, there is a body of evidence identifying a large number of prescribed drugs and major polypharmacy (i.e. concomitant use of ≥9 medications) as predictors for pDDIs (Sharma, Chhetri, Alam, 2014; Rodrigues et al., 2017; Jain et al., 2017; Dookeeram et al., 2017). However, as mentioned earlier, both of these factors showed a slightly significant difference between patients who experienced pCDDIs and those without such outcome in the univariate logistic regression model, but after the adjustment for other covariates, their effects disappeared. Obviously, when combined, these factors do not act independently in terms of increasing the likelihood of pCDDIs in this population of severely ill patients unmatched by relevant confounders. Nevertheless, longer duration of the hospitalization could be considered a proxy risk factor for a large number of prescribed drugs in its predominant contribution to pCDDIs. In addition, patients who used multiple drugs from different therapeutic/pharmacological subgroups according to ATC classification, were somewhat more likely to be exposed to pCDDIs, indicating physicians’ propensity to treat the symptoms of the disease exclusively and a well-known rule of combined pharmacotherapy regarding the use of therapeutic alternatives with different mechanisms of action.

Studies have shown that less than 20% of patients with sICH usually receive prophylactic anticoagulant therapy (Prabhakaran et al., 2015). Based on the available literature evidence, it is safe to introduce this therapy after 48 hours of the admission in patients with stable hematoma who have a more severe clinical picture and a high risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) (Dastur, Yu, 2017). Anticoagulant therapy has a significant role in pDDIs (Tesfaye, Nedi 2017; Colet, Amador, Heineck, 2019), especially when it comes to clinically relevant drug interactions (Vazquez, 2018). For example, warfarin is recognized as a drug that has numerous interactions and 99.2% of hospitalized patients who were prescribed this anticoagulant, were exposed to pDDI, 16% of whom experienced gastrointestinal bleeding as a complication (Teklay et al., 2014). In a study with direct oral anticoagulants (DOAC), 37% of elderly hospitalized patients were exposed to pDDIs, most of them with a risk of bleeding (Forbes, Polasek, 2017). Medications that may increase the risk of bleeding should be discontinued prior to the initiation of low-molecular-weight-heparins (LMWH), if the patient’s health condition allows. These drugs include anticoagulants, acetylsalicylic acid, and NSAIDs. If co-administration is strictly indicated, close clinical and laboratory monitoring of patients is required (Lovenox, 2009). Fewer of our patients received sequentially LMWH (enoxaparin) and warfarin, and there were no patients with DOAC. The decision to administer anticoagulant therapy in patients with sICH is rather complicated and associated with numerous challenges. It is necessary to consider all relevant factors: the severity of the patient’s
CONCLUSION

This study suggests that pDDIs are highly prevalent in patients with sICH. Of particular importance is also relatively common occurrence of the most dangerous pCDDIs that are strongly related to poor clinical outcomes. The use of anticoagulant therapy appears to be the only modifiable clinically relevant predictor of pCDDIs. This places great caution when prescribing any new anticoagulant drug in patients with sICH, imposing intensive clinical and therapeutic monitoring when using these medications in everyday practice. To prevent poor treatment outcomes, neurologists and intensivists should always be aware of possible drug-drug interactions during the treatment of seriously ill patients in intensive care units, especially when multiple drugs are used, including both oral and parenteral anticoagulants.

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