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Delays in Intracerebral Hemorrhage Management Is Associated with Hematoma Expansion and Worse Outcomes: Changes in COVID-19 Era

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Purpose: The coronavirus disease 2019 (COVID-19) pandemic disrupted the emergency medical care system worldwide. We analyzed the changes in the management of intracerebral hemorrhage (ICH) and compared the pre-COVID-19 and COVID-19 eras.
Materials and Methods: From March to October of the COVID-19 era (2020), 83 consecutive patients with ICH were admitted to four comprehensive stroke centers. We retrospectively reviewed the data of patients and compared the treatment workflow metrics, treatment modalities, and clinical outcomes with the patients admitted during the same period of pre-COVID-19 era (2017–2019).
Results: Three hundred thirty-eight patients (83 in COVID-19 era and 255 in pre-COVID-19 era) were included in this study. Symptom onset/detection-to-door time [COVID-19; 56.0 min (34.0–106.0), pre-COVID-19; 40.0 min (27.0–98.0), p=0.016] and median door to-intensive treatment time differed between the two groups [COVID-19; 349.0 min (177.0–560.0), pre-COVID-19; 184.0 min (134.0–271.0), p<0.001]. Hematoma expansion was detected more significantly in the COVID-19 era (39.8% vs. 22.1%, p=0.002). At 3-month follow-up, clinical outcomes of patients were worse in the COVID-19 era (Good modified Rankin Scale; 33.7% in COVID-19, 46.7% in pre-COVID-19, p=0.039).
Conclusion: During the COVID-19 era, delays in management of ICH was associated with hematoma expansion and worse outcomes.

Key Words: COVID-19, hemorrhage, incidence, stroke

INTRODUCTION

On March 11, 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) outbreak a pandemic.[1] Many countries have tried to prevent the spread of COVID-19 by avoiding physical contact and improving personal hygiene in public life. In medical institutions, further restrictions have also been implemented under limited resources, and most medical resources have been used to cope with the COVID-19 pandemic. However, these efforts to prevent the spread of COVID-19 caused significant changes in the diagnosis and treatment processes of acute illness in the clinical field.[2,3] Similarly, changes in the management of acute stroke care have also been reported in recent studies.[4,5] However, these previous studies mainly focused on patients with acute ischemic stroke, not with acute hemorrhagic stroke.

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Spontaneous intracerebral hemorrhage (ICH) is a disease that accounts for up to 24% of hemorrhagic strokes and can be fatal with a 1-month mortality rate of up to 40%.[6-9] High blood pressure and hematoma expansion are associated with poor functional outcomes or death after ICH.[10-12] Therefore, patients with ICH require acute intensive management regarding blood pressure and intracranial pressure to reduce the risk of a fatal outcome. As a result, management in the intensive care unit (ICU) is essential for patients with ICH.[11-14] However, a significant amount of medical resources is being consumed for the treatment of COVID-19, and little is known about the effect of this uneven distribution of resources on the acute management of ICH in the COVID-19 era.

Globally, studies are being initiated in patients with acute hemorrhagic stroke.[15,16] However, these studies have only shown the incidence of hemorrhagic stroke in patients with COVID-19, and information pertaining to the impact of COVID-19 on the treatment of hemorrhagic stroke is still lacking.

Therefore, in the present study, we aimed to evaluate and compare the changes in the management of ICH between the pre-COVID-19 and COVID-19 eras.

MATERIALS AND METHODS

Study design

Institutional Review Board of Catholic Kwandong University (IS20EIME0065), Yonsei University Severance Hospital (4-2020-0577), Yonsei University Gangnam Severance Hospital (3-2020-0364) and the National Health Insurance Service (NHIS) (NHIMC 2021-07-039) approved this study. Also, the need to obtain patient informed consent was waived because of the retrospective study design. The study was performed under the guidelines outlined by the Declaration of Helsinki, and the manuscript followed the STROBE checklist.

Patient population

In this study, we defined the COVD-19 era as the period from March to October 2020, whereas the same period during the preceding three years i.e., March to October in 2017, 2018, and 2019 is defined as the pre-COVID-19 era. Overall, during the pre-COVID-19 and COVID-19 eras, a total of 560 patients were admitted with ICH to four comprehensive stroke centers. Among them, the following patients were excluded: 1) patients aged <18 years; 2) patients who were transferred from another hospital under previous intensive treatment; 3) those whose diagnosis was delayed by >6 hours after symptom onset; and 4) those with ICH due to aneurysm, arteriovenous malformation, or any vasculopathy. Finally, 338 patients (83 in the COVID-19 era and 255 in the pre-COVID-19 era) were included in this study.

All clinical and radiological data were obtained from electronic medical records and retrospectively reviewed and compared between the COVID 19 and pre-COVID-19 era.

COVID-19 prevention guidelines

On February 20, 2020, the Korea Centers for Disease Control and Prevention issued guidelines on screening for COVID-19 in emergency departments.[17] According to the guidelines, a screening test of COVID-19 should be performed through a separate triage space for suspected patients with 1) pneumonia of unknown cause, 2) respiratory symptoms with a recent visit to a contaminated area within 14 days, or 3) respiratory symptoms with recent contact with a COVID-19 (+) patient within 14 days.

Additionally, basic precautionary measures should be implemented for all suspected patients, and contact and airborne precautions are to be applied depending on the situation (Fig. 1). COVID-19 (+) or suspected patients should be isolated and treated in a negative pressure room within a triage space in the emergency department. Only authorized healthcare personnel can contact the COVID-19 (+) or suspected patient while wearing personal protective equipment. If the patient requires surgical or interventional treatment, intubation should be performed only by authorized healthcare personnel in a negative-pressure room or in an air-exchange room at least 12 times per

Shorter distance from patients/Higher risk of contamination

Basic precaution

- A mask should be put on the suspected patient while the patients is temporarily under quarantine in a separate place.
- Suspected patients should maintain a distance of at least 1 meter from other patients.
- All patients should be instructed to fold their tissues or arms to cover their nose and mouth when coughing or sneezing.
- Hand hygiene should be performed after contact with respiratory secretions.

Contact precaution

- Contact caution prevents both direct and indirect spread of the disease that occurs through contact with contaminated surfaces or materials.
- When entering a hospital room, physicians should wear personal protective equipment (mask, eye protection, gloves, and gown) and remove the personal protective equipment before leaving the room.
- If possible, use disposable equipment (e.g., stethoscope, cuff, thermometer, etc.).
- When items (devices) are shared among patients, each item should be cleaned and disinfected before use.
- Patients' movement or transportataion is restricted and allowed only when absolutely necessary.

Airborne precaution

- In the event of possible aerosol generation (open air suction, tracheal intubation, bronchoscopy, cardiopulmonary resuscitation, etc.), medical practitioners should wear gloves, long-sleeved gowns, eye protection, and fit-tested respiratory protection (N95 mask) as personal protective equipment.
- If possible, patients should be managed in a room with air exchange 12 times an hour.
- Only essential personnel should be allowed in the negative-pressure containment room.
- After starting mechanical ventilation, the patient should be managed in a quarantine room with equal ventilation.

Fig. 1. Korea Centers for Disease Control and Prevention guidelines for COVID-19 in medical institutions. COVID-19, coronavirus disease 2019.

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hour. As the number of healthcare personnel participating in the surgery or intervention is limited, all of them should wear personal protective equipment (full-body protective clothing, N95 masks, gloves, hats, goggles, or face shields); powered air-purifying respirators may be used, if possible. Then, the COVID-19 (+) or suspected patient should be treated in a specialized ward or ICU for COVID-19. After the confirmation of COVID-19 (-), all processes should be routinely conducted in the usual manner. The four comprehensive stroke centers participating in this study followed all of the aforementioned guidelines.

Image study analysis

Based on the protocol of the institution, follow-up computed tomography (CT) images were obtained after admission to evaluate hematoma expansion. Most patients had a follow-up CT scan performed on the following day, 12–24 hours after symptom onset/detection, unless their neurologic status worsened or they were suspected to have experienced a change in their intracranial pressure. ICH volume was defined using the ABC/2 formula, and assessed at the time of each CT scan. Hematoma expansion was determined as an increase in the initial volume by >33% or an increase of hematoma volume by >6 mL in the follow-up CT scan, as reported in previous studies.[18-21] The image acquisition, measurement, and analysis were conducted by three independent investigators (H.J.H, Y.H.L, and S.Y.K). In case of disagreement, another neurosurgeon (K.Y.P) reviewed the data, and four investigators decided on the final results with consensus.

Outcome measurements

The following workflow metrics (measured in minutes) of each patient were evaluated: 1) symptom onset/detection-to-door time; 2) door-to-imaging time; 3) door-to-intensive treatment time; and 4) overall symptom onset/detection-to-intensive treatment time. Intensive treatment was defined as the best medical treatment for managing blood pressure and intracranial pressure, correction of coagulopathy, or reversal of anticoagulants in the neuro-critical care unit. Surgical treatment was also divided into catheter surgery and open surgery. At the 90-day follow-up, functional outcome was assessed by experienced neurosurgeons or rehabilitation medicine physicians using the modified Rankin Scale (mRS). An unfavorable outcome was defined as mRS score of 3 or more. All variables were compared between the COVID-19 and pre-COVID-19 groups.

Statistical analyses

For comparison between the two groups, univariate analysis was performed using chi-squared test, Fisher's exact test, Mann–Whitney U test, and standard t-tests. Multivariable analysis was performed on variables with a $p<0.10$ on univariate analysis. Binary logistic regression analysis was used to perform multivariable analysis for hematoma expansion and 90-day functional outcome. Significance was defined as $p<0.05$. Statistical analyses were performed using IBM SPSS Statistics version 25.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

During the COVID-19 era, 83 patients (average age of 63.4 years) were treated for ICH in four comprehensive stroke centers. In the same period during the pre-COVID-19 era, 255 patients (85 patients/year, average age of 60.7 years) were treated for ICH in the same centers. There were no significant differences in baseline characteristics, medical history, or initial GCS between the two groups (Table 1).

Regarding workflow metrics, symptom onset/detection-to-door time was significantly different between the two groups [COVID-19; 56.0 min (34.0–106.0), pre-COVID-19; 40.0 min (27.0–98.0), $p=0.016$]. Door-to-imaging time did not significantly differ between the two groups, but showed a tendency to delay in the COVID-19 group [COVID-19; 24.0 min (15.0–38.0), pre-COVID-19; 20.0 min (13.0–32.0), $p=0.082$]. Door-to-intensive treatment time [COVID-19; 349.0 min (177.0–560.0), pre-COVID-19; 184.0 min (134.0–271.0), $p<0.001$] showed a significant delay during the COVID-19 era. Finally, the overall symptom onset/detection-to-intensive treatment time was significantly delayed in the COVID-19 group [COVID-19; 430.0 min (248.0–640.0), pre-COVID-19; 255.0 min (189.0–375.0), $p<0.001$] (Table 2 and Fig 2).

Table 3 shows a comparison of the characteristics of the hematoma expansion (+) and (-) groups. Previous cerebrovascular accident (CVA) history ($p<0.001$), antithrombotic usage ($p<0.001$), initial GCS ($p=0.011$), and delayed door-to-intensive treatment time ($p=0.046$) were risk factors related to hematoma expansion. In the multivariable logistic regression analysis, previous cerebrovascular accident (CVA) history [odds ratio (OR): 2.818, 95% confidence interval (CI): 1.438–5.522]; low initial GCS (OR: 1.108, 95% CI: 1.037–1.184); and delayed door-to-intensive treatment time (OR: 0.998, 95% CI: 0.997–1.000)

Table 1. Baseline Characteristics and Risk Factors of Intracerebral Hemorrhage Patients

	COVID-19 (n=83)	Pre-COVID-19 (n=255)	*p* value
Age, yr	63.4 (14.4)	60.7 (16.4)	0.185
Sex, male	43 (51.8)	148 (58.0)	0.320
Medical history			
Hypertension	48 (57.8)	149 (58.4)	0.923
Current smokers	32 (38.6)	90 (35.3)	0.591
Antithrombotic usage	27 (32.5)	66 (25.9)	0.239
Previous CVA	20 (24.1)	54 (21.2)	0.576
Initial GCS	11.6 (4.00)	10.9 (4.30)	0.175

COVID-19, coronavirus disease 2019; SD, standard deviation; CVA, cerebrovascular accident; GCS, Glasgow Coma Scale.
Data are presented as mean (SD) or n (%).

Table 2. Workflow Metrics, Treatment Details, and Clinical Outcomes

	COVID-19 (n=83)	Pre-COVID-19 (n=255)	*p* value
Symptom onset/ detection-to-door time	56.0 (34.0–106.0)	40.0 (27.0–98.0)	0.016*
Door-to-imaging time	24.0 (15.0–38.0)	20.0 (13.0–32.0)	0.082
Door-to-intensive treatment time	349.0 (177.0–560.0)	184.0 (134.0–271.0)	<0.001*
Symptom onset/detection-to-intensive treatment time	430.0 (248.0–640.0)	255.0 (189.0–375.0)	<0.001*
Hematoma expansion†	33 (39.8)	47 (22.1)	0.002*
Treatment modality			0.180
Medical intensive care	56 (67.5)	151 (59.2)	
Surgical treatment	27 (32.5)	104 (40.8)	
Surgical treatment			0.170
Catheter surgery	18 (66.7)	54 (51.9)	
Open surgery	9 (33.3)	50 (48.1)	
90-day functional outcome			0.039*
Unfavorable (mRS ≥3)	55 (66.3)	136 (53.3)	

COVID-19, coronavirus disease 2019; IQR, iterquartile range; mRS, modified Rankin Scale.
Workflow metrics measured in minutes. Data are presented as median (IQR) or n (%).
*Statistically significant, †296 patients could be included for hematoma expansion analysis.

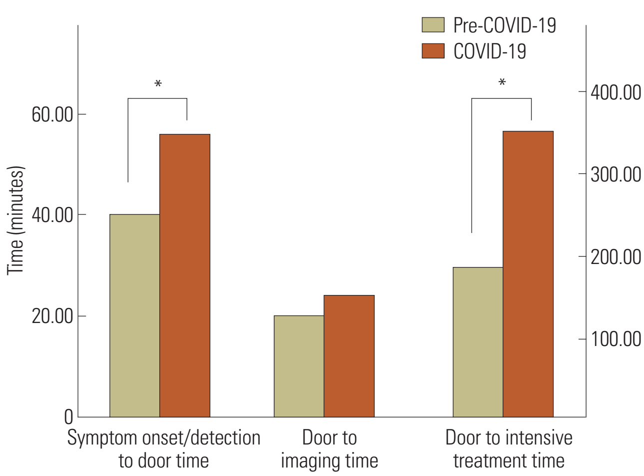

Fig. 2. Comparison of workflow metrics in the management of ICH between COVID-19 and pre-COVID-19 eras. The symptom onset/detection-to-door time was significantly different between the two groups [COVID-19; 56.0 min (34.0–106.0), pre-COVID-19; 40.0 min (27.0–98.0), *p*=0.016]. Also, door-to-intensive treatment time [COVID-19; 349.0 min (177.0–560.0), pre-COVID-19; 184.0 min (134.0–271.0), *p*<0.001] showed a significant delay during the COVID-19 era. **p*-value considered statistically significant. COVID-19, coronavirus disease 2019; ICH, intracerebral hemorrhage.

were significant independent risk factors for hematoma expansion (Table 4).

At the 90-day follow-up visit (available in all patients), patients in the COVID-19 group had a worse functional outcome compared to those in the pre-COVID-19 group (Table 5 and Fig. 3). In the analysis restricted to patients who were independent, 55 patients (66.3%) in the COVID-19 group and 136 patients (53.3%) in the pre-COVID-19 group had an unfavorable mRS score (≥3) (*p*=0.039). In the multivariable logistic regression analysis, COVID-19 era (OR: 3.122, 95% CI: 1.571–6.203); low initial GCS (OR: 0.663, 95% CI: 0.593–0.741); hematoma expansion (OR: 2.003, 95% CI: 1.004–3.997); medical intensive care (OR: 4.057, 95% CI: 1.984–8.298); and older age (OR: 1.038, 95% CI: 1.017–1.060) were independent predictors of an unfavorable functional outcome at 90 days (Table 5).

Table 3. Comparison between Hematoma Expansion (+) vs. (-) Subgroups

	Hematoma expansion (+) (n=80)	Hematoma expansion (-) (n=216)	*p* value
Age, yr	63.1 (14.4)	61.5 (16.3)	0.420
Sex, male	50 (62.5)	118 (54.6)	0.225
Medical history			
Hypertension	50 (62.5)	125 (57.9)	0.472
Current smokers	36 (45.0)	77 (35.6)	0.141
Antithrombotic usage	37 (46.3)	48 (22.2)	<0.001*
Previous CVA	34 (42.5)	37 (17.1)	<0.001*
Initial GCS	10.0 (4.23)	11.4 (4.22)	0.011*
Symptom onset/detection-to-door time, median (IQR)	41.5 (28.3–83.3)	51.0 (30.0–118.5)	0.152
Door-to-imaging time, median (IQR)	20.0 (13.0–32.0)	20.0 (13.0–31.0)	0.478
Door-to-intensive treatment time, median (IQR)	219.0 (151.0–395.0)	194.0 (134.0–295.0)	0.046*
90-day functional outcome			0.003*
Unfavorable (mRS ≥3)	57 (71.3)	113 (52.3)	

SD, standard deviation; CVA, cerebrovascular accident; GCS, Glasgow Coma scale; IQR, interquartile range; mRS, modified Rankin Scale.
Workflow metrics measured in minutes. Data are presented as mean (SD) or n (%).
*Statistically significant.

Table 4. Multivariable Analysis of Hematoma Expansion

	Multivariable analysis	
	OR	95% CI
Antithrombotic usage	1.780	0.942–3.363
Previous CVA history	2.818	1.438–5.522
Initial GCS	1.108	1.037–1.184
Symptom onset/detection-to-door time	1.001	0.997–1.004
Door-to-intensive treatment time	0.998	0.997–1.000

OR, odds ratio; CI, confidence interval; CVA, cerebrovascular accident; GCS, Glasgow Coma Scale.

DISCUSSION

During the last year of the COVID-19 pandemic, 2020, governments and medical institutions have done their best to pre-

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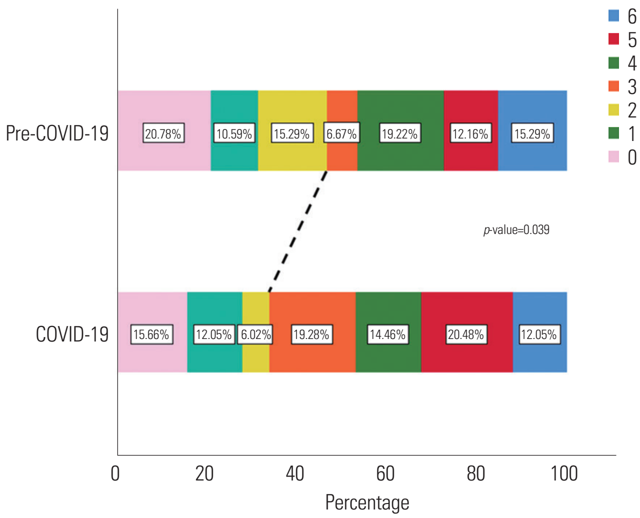

Fig. 3. Comparison of the 90-day functional outcomes between COVID-19 and pre-COVID-19 eras. COVID-19, coronavirus disease 2019.

Table 5. Univariate and Multivariable Regression Analyses of Unfavorable Functional Outcomes at 90 Days

	Univariate analysis		Multivariable analysis	
	OR	95% CI	OR	95% CI
COVID-19 era	1.719	1.025–2.883	3.122	1.571–6.203
GCS	0.635	0.573–0.703	0.663	0.593–0.741
Hematoma expansion (+)	3.641	2.142–6.191	2.003	1.004–3.997
Medical intensive care	8.811	5.072–15.305	4.057	1.984–8.298
Age	1.018	1.004–1.032	1.038	1.017–1.060

OR, odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; GCS, Glasgow Coma Scale.

vent the spread of COVID-19 around the globe. However, in conjunction with these efforts, the pandemic might affect the management of patients with acute illness due to limited medical resources, the overload in public healthcare, and inordinate public fear of COVID-19. Consistent with these limitations, Tam, et al.[3] detected a significant time delay in the management of acute ST-segment–elevation myocardial infarction, and Schrag et al.[2] predicted that rapid changes in oncology practice would occur due to the prevention of COVID-19 spread, remote management, and consecutive treatment omission or delay.

Despite the COVID-19 outbreak, many stroke experts have tried to maintain acute stroke care and proposed modified algorithms in the current situations.[22,23] Smith, et al.[23] designed an algorithm for acute stroke care according to the airway maintenance requirements, resources availability, and stability for transport. Nguyen, et al.[22] suggested that thrombectomy should be performed with the minimum number of medical personnel under protection, using communication equipment such as telecommunication and environmental management. Lastly, a recent study has shown that there was no delay in acute stroke management, including in-hospital workflow metrics.[24] Unfortunately, such efforts were mainly limited to acute ischemic stroke management, as only few hospitals have protocols specific to the management of ICH comparing with acute ischemic stroke.[25]

Several studies also reported that the COVID-19 pandemic decreased the number of hospital admissions and reperfusion therapy. In a study by Rudilosso, et al.[4] in March 2020, the number of stroke codes in Catalonia declined by 23% compared to that of March 2019 (p=0.009). In another study by Zhao et al.,[26] a significant decrease in reperfusion therapy in China was reported (p<0.0001), and it was suggested that the potential reason for the decreased number of stroke patients was a "fear of contracting COVID-19 in hospital."[27] On the other hand, in the present study, the number of hospital admissions during the COVID-19 era (2020) was not different compared to the same period during the pre-COVID-19 era (2017–2019). It remains uncertain as to why the number of patients with ICH did not decrease during the COVID-19 era, unlike of those with acute ischemic stroke or coronary disease. In our theory, it is because patients with ICH present with more severe neurological status, and many patients or their legal representatives might have a "fear of fatality due to hemorrhagic stroke" rather than a "fear of contracting COVID-19 in hospital." This result was also supported by a study by Diegoli, et al.,[28] in which the number of admissions for ischemic stroke was significantly decreased in Joinville, but that for hemorrhagic stroke, including intraparenchymal and subarachnoid hemorrhage, was not different between the pre-COVID-19 and COVID-19 eras.

In the present study, the ICH patient group of the COVID-19 era showed a significant time delay in both symptom onset-to-intensive treatment time and door-to-intensive care time. In subgroup analysis, the door-to-intensive treatment time was markedly increased in patients whose history was unclear or those who were suspected of being infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), compared to the patients not suspected to be infected (427.3 minutes and 207.8 minutes, respectively). In the emergency room, the waiting time for the SARS-CoV-2 test result or for available ICU beds among those categorized as possible COVID-19 patients might be increased. Generally, if the operation of an emergency department focuses on the prevention of SARS-CoV-2 transmission, this affects the treatment process of many acute illnesses, including the workflow of ICH management. Since there was no secured transport pathway from the emergency room to the operating room and from the operating room to the ICU, delays in patient transfer were unavoidable. The changes introduced in the COVID-19 era led to delays, which resulted in hematoma expansion.

Hematoma expansion, one of the major concerns of acute ICH management, occurred more frequently during the COVID-19 era, which led to a poorer clinical outcome than in the pre-COVID-19 era. In the literature, hematoma expansion is known to occur in up to 30% of patients, and several studies have suggested that intensive treatment, including blood pressure control, reversal of coagulopathy, and surgical treatment, can increase the chance of a better clinical outcome in patients with ICH.[29-32] However, in the COVID-19 era, the choice between open craniotomy and catheter surgery was also a major concern. Clinician's protection, ventilation and disinfection of operative rooms, and secured transport pathways were also considered in surgical decision-making. In this study, we had to decide which surgery to perform in two ICH patients who were suspected to have COVID-19. Open craniotomy could not be performed, as the surgeons could not access the microscope while wearing personal protective equipment, and both patients experienced unfavorable 90-day functional outcomes.

In terms of clinical outcome, the functional outcome at 90 days of ICH patients was worse in the COVID-19 era than in the pre-COVID-19 era. In the multivariable analysis, an unfavorable 90-day functional outcome was associated with low GCS, medical intensive care only, and advanced age. The association between advanced age and poor functional outcome at 90 days might be due to some older patients with large hematomas refusing surgical treatment. More importantly, hematoma expansion and the COVID-19 era were associated with unfavorable functional outcomes at 90 days, and delay of door-to-intensive care time was a significant risk factor for hematoma expansion. In the COVID-19 era, delay in the emergency room and interference of ICH workflow might lead to hematoma expansion; as a result, the overall changes might be associated with unfavorable clinical outcomes.

To our knowledge, the present study is the first regarding delays in the management of patients with ICH in the COVID-19 era. However, our study had several limitations. First, due to the limitations inherent in the retrospective design with short-term follow-up, a selection bias was inevitable regarding the demographics and percentages observed. Second, the population of this study was limited to the specific area of South Korea. Therefore, our results cannot be generalized and directly applied to other areas or countries around the world. Also, the ICH and hematoma expansion volume could not be measured, and accurate records of the CT follow-up time could not be obtained. Nevertheless, to the best of our knowledge, this study is the first and the largest study on ICH management in the COVID-19 pandemic, and could be helpful in evaluating stroke management in the COVID-19 era in future studies.

These results illustrate the adverse effect of non-standardized ICH management in the COVID-19 era on functional outcomes as a consequence of changes in the workflow metrics and increased hematoma expansion. During the COVID-19 era, ICH management was delayed, and hematoma expansion occurred more frequently. Furthermore, clinical outcomes were significantly different from those of the pre-COVID-19 era. Considering the results of this study, the treatment process for ICH patients in the COVID-19 era should be reviewed, and developing a special intensive care protocol for ICH patients should be considered.

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AUTHOR CONTRIBUTIONS

Conceptualization: Hyun Jin Han, Keun Young Park, and So Yeon Kim. Data curation: Junhyung Kim, Woosung Lee, and Yun Ho Lee. Formal analysis: Hyun Jin Han. Investigation: Hyun Jin Han. Methodology: Keun Young Park, Junhyung Kim, Woosung Lee, Yun Ho Lee, and So Yeon Kim. Project administration: Keun Young Park, Kwang-Chun Cho, Chang Ki Jang, Sang Kyu Park, Joonho Chung, Young Sub Kwon, Yong Bae Kim, Jae Whan Lee, and So Yeon Kim. Resources: Keun Young Park, Junhyung Kim, Woosung Lee, Kwang-Chun Cho, Yun Ho Lee, Chang Ki Jang, Sang Kyu Park, Joonho Chung, Young Sub Kwon, Yong Bae Kim, Jae Whan Lee, and So Yeon Kim. Software: Hyun Jin Han. Supervision: Keun Young Park and So Yeon Kim. Validation: Junhyung Kim, Woosung Lee, Yun Ho Lee, and So Yeon Kim. Visualization: Hyun Jin Han. Writing—original draft: Hyun Jin Han. Writing—review & editing: So Yeon Kim. Approval of final manuscript: all authors.

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