



# Retrospective Examination of Patients with Spontaneous Cranial Intracerebral Hematoma

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## ABSTRACT

**AIM:** To investigate the relationship among the modified Rankin scores of patients who had intracerebral hematomas at discharge, demographic characteristics of the patients, and the characteristics of the hematoma.

**MATERIAL and METHODS:** In this study, patients diagnosed with intracerebral hematoma and treated at the Ministry of Health Ankara Training and Research Hospital Neurosurgery Clinic between January 2010 and December 2020 were examined retrospectively. The age, gender, comorbidity, anticoagulant-antiaggregant use, and Glasgow Coma Scale score of the patients were obtained from hospital records. The modified Rankin scale (mRS) was used to assess patients at discharge.

**RESULTS:** Herein, a total of 114 patients with supratentorial intracerebral hematoma were evaluated. The modified Rankin score ranged from 0 to 6, with a mean score of  $3.47 \pm 2.26$ . When the patients were evaluated based on their discharge status, the mortality rate was 33.3% (n=38). Fifty percent of the patients who used anticoagulant-antiaggregant died. High mRS scores were seen more frequently in advanced age. Among the other diseases of the patients, hypertension and the use of anticoagulant-antiaggregant were found to be statistically significant with high mRS scores ( $p<0.001$ ). Patients with low Glasgow Coma Scale score at the time of admission had significantly higher mRS scores ( $p<0.001$ ).

**CONCLUSION:** Patients with advanced age, hypertension, and anticoagulant-antiaggregant use had a higher mRS score after hematoma formation. Preventable risk factors for spontaneous intraparenchymal hematomas are among the leading causes of disability, and early detection and treatment of underlying diseases are critical for hematoma prevention. Awareness about risk factors should be the priority to improve early diagnosis and reduce treatment disability rates.

**KEYWORDS:** Intracerebral hematoma, Modified Rankin Scores, Prognosis

## INTRODUCTION

Spontaneous intracerebral hematoma is an important cause of morbidity and mortality on a global scale (6). Although hypertension is the most common cause of primary hematomas; secondary hematomas can also be caused by vascular abnormalities, tumors, embolism-related

diseases, and treatment processes (16). The incidence of spontaneous intracerebral hemorrhage is 15-19/100.000/year and 30-day mortality is 40-50% (1). The average annual mortality rate in surviving patients was 8%, and these deaths are frequently associated with neurological sequelae (7). Hypertension, advanced age, male gender, anticoagulation

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therapy, smoking, and diabetes were identified as risk factors (1,6,28,33). Determining these risk factors is crucial for the development of preventive measures.

Patients with spontaneous intracranial hematomas undergo different surgical procedures, such as open craniotomy, decompressive craniectomy, minimally invasive approaches, and neuro endoscope-guided hematoma evacuation (9).

Many scoring systems were developed for both evaluating the prognosis and determining the surgical decision in patients who were diagnosed with hematoma. In intracerebral hemorrhage scoring system, the patient is scored according to the Glasgow Coma Scale (GCS) score, hematoma volume, spread to the intraventricular region, infratentorial location, and age of the patient (17). The modified Rankin scale (mRS) is a disability assessment method used to evaluate patients with cerebrovascular diseases. It provides information about a patient's level of disability as a result of stroke and is useful for both monitoring and making prognostic predictions. Low scores indicate a low rate of disease-related disability, although high scores indicate severe disability or death from stroke. A score of zero indicates that the patient has no symptoms and can resume his normal life following the stroke (25).

The goal of this study was to look into the relationship among the modified Rankin scores of patients who had intracerebral hematomas at discharge, the demographic characteristics of the patients, and the characteristics of the hematoma.

## MATERIAL and METHODS

Our study was approved by the Ministry of Health, Ankara Training and Research Hospital, Clinical Research Ethics Committee, dated 20/08/20 and numbered E-20.

The patients diagnosed with intracerebral hematoma and treated at the Ministry of Health Ankara Training and Research Hospital neurosurgery clinic between January 2010 and December 2020 were studied retrospectively. Based on the hematoma location of the patients, those who had infratentorial hematoma were excluded from the further analysis. The patients were classified as having primary or secondary spontaneous intracerebral hematomas. The age, gender, comorbidity, and anticoagulant-antiaggregant use of the patients were obtained from hospital records. The GCS was used to assess the patient's neurological status.

The intracerebral hematoma (ICH) was divided into two groups according to localization as supratentorial and infratentorial status in the study. Supratentorial hemorrhages were classified as either lobar (cortex-subcortical white matter) or deep (internal capsule, basal ganglia, and periventricular white matter), whereas infratentorial hemorrhages were classified as cerebellar or brainstem hemorrhages. Bleeding volumes were calculated using the ellipsoidal method. The volume of a hematoma influences the course of the disease. Computerized methods can be used to calculate the hematoma volume. It can also be calculated using the ABC/2 method. A is the maximum diameter of the hematoma in the reference section with the most hematoma area. B is the

hematoma's perpendicular diameter to the largest diameter in this reference section, and C is the number of sections (1,6,26,30).  $(A \times B \times C \times 1/2) = A$ : width, B: length, C: height (Figures 1 and 2).

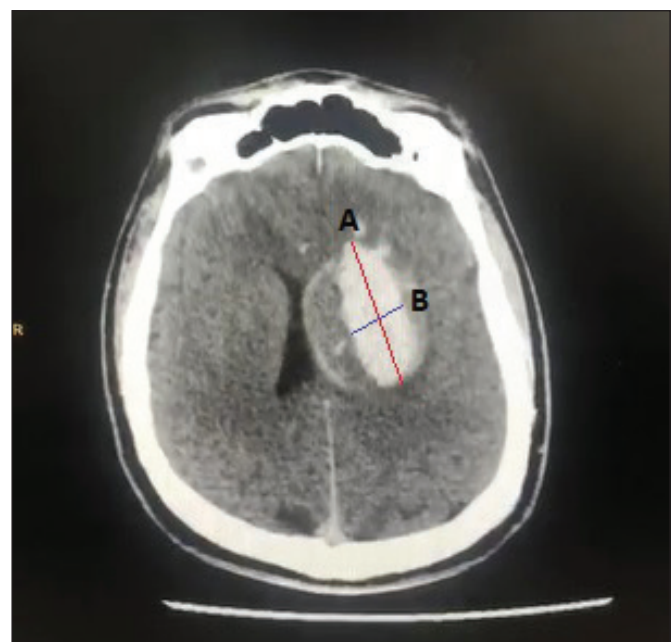
In computerized brain tomography, the location and size of the hematoma, whether it opened to the ventricles, the mid-line shift measurement, and the formation change in the 4<sup>th</sup> ventricle in infra-tentorial hematomas were examined and measured. The intracerebral hemorrhage score (IHS) of the patients was calculated by examining the file information. Pathological conditions detected in other radiological examinations for the diagnosis were determined in the patient who was thought to have a secondary spontaneous intracerebral hematoma. The mRS was used in the evaluation of patients at discharge.

## Statistical Analysis

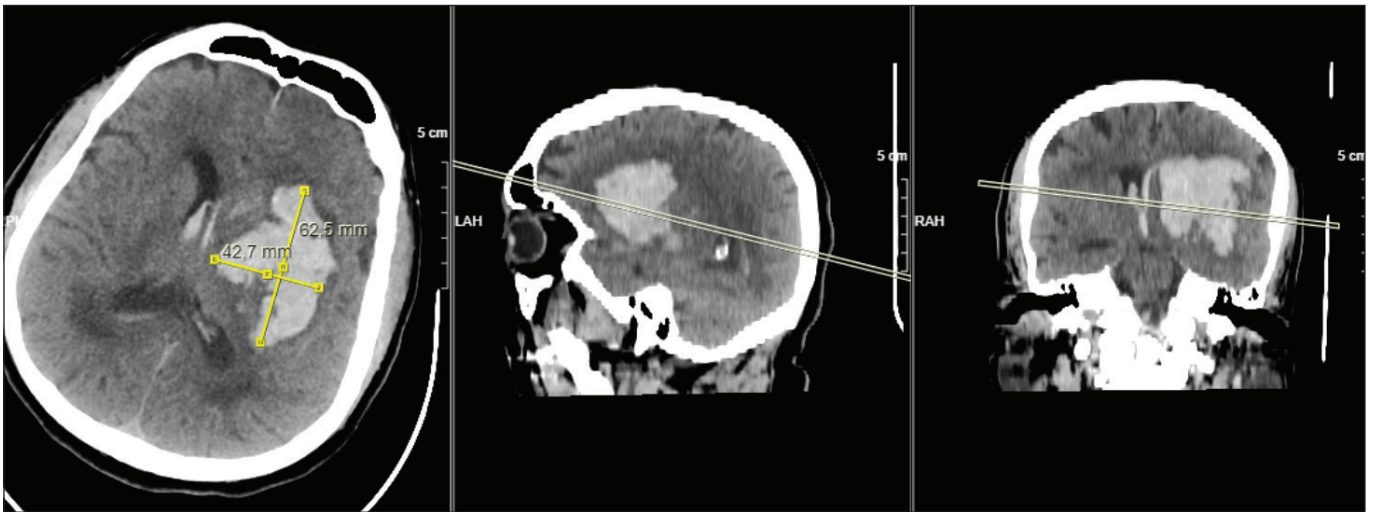
The chi-square test was used for descriptive statistics (number, percentage, mean and standard deviation) and numerical variables in statistical analysis. Statistical data were evaluated using the SPSS 20.0 package program. P value of <0.05 was considered significant.

## RESULTS

A total of 129 patients with intracerebral hematomas, including 58 women (44.96%) and 71 men (55.03%) were included in this study. Fifteen of these patients were excluded from the study because of the presence of infratentorial hematomas and a total of 114 patients were evaluated. The patient's age ranging 25–90 years, with a mean of 59.8 years were considered. Patients were divided into three groups according to their ages; <55 years, 56–75 years, and >76 years. When the age distributions were examined, 31.5% of the patients



**Figure 1:** Supratentorial left thalamic hematoma.



**Figure 2:** Supratentorial left thalamic hematoma.

(n=36) were under the age of 55, 43% (n=49) were between the age of 56–75, and 25.5% (n=29) were 75 or older. In 40 (35%) patients, hypertension was detected. Antiaggregant–anticoagulant therapy was used by 44 patients. The mean hematoma volume was 40.8 cm<sup>3</sup> (range: 1–136.5 cm<sup>3</sup>). When the hematomas were classified by volume, 38.5% (n=44) had a hematoma volume less than 30 cm<sup>3</sup>, 24.5% (n=28) had between 30–50 cm<sup>3</sup>, and 37% (n=42) had greater than 50 cm<sup>3</sup>. Table I shows the demographic characteristics of the patients based on their primary and secondary hematomas status. The modified Rankin score ranged from 0 to 6, with a mean score of  $3.47 \pm 2.26$ . At the end of the treatment, 49.1% (n=56) of the patients had a poor prognosis and 50.9% (n=58) had a good prognosis based on the mRS score ( $\leq 3$  as a good prognosis and  $>3$  as a bad prognosis). Twenty-six (46.4%) of the 56 patients with a poor prognosis were female, while 30 (53.5%) were male. Twenty-seven (46.5%) of the 58 patients with a good prognosis were female, while 31 (53.5%) were male (Table II). No significant differences were detected between the sexes in terms of prognosis ( $p=0.714$ ).

When the patients were evaluated based on their discharge status, it was found that 38 of them died. The mortality rate was 33.3% in the present study. Table III shows the demographic characteristics of the patients based on their mortality status as well as their hematoma characteristics. Nearly 50% of the patients who used anticoagulant–antiaggregant died. In terms of mean hematoma volume, the patient group that did not survive had a hematoma volume of 55.2 cm<sup>3</sup>, while the patient group that did survive had 39.4 cm<sup>3</sup>.

Surgery was performed in 68 patients and external ventricular drainage (EVD) was performed in 4 patients. In our study, the hematoma volume was less than 30 cm<sup>3</sup> in 11 of the 68 patients who underwent surgery, between 30–50 cm<sup>3</sup> in 21, and greater than 50 cm<sup>3</sup> in 36. In addition, hematoma volume is below 30 cm<sup>3</sup> in all patients treated with EVD. Surgery was not performed on 41 patients because they were not surgical candidates, and one patient refused surgery despite being offered. These patients were followed-up. The characteristics

of the patients are given in Table I according to primary and secondary hematoma status. There was significant difference between the distribution of age groups and mRS. Elevated mRS scores were seen more frequently in advanced age. Among the patient's additional diseases, hypertension, and anticoagulant–antiaggregant use were statistically significant with high mRS scores ( $p<0.001$ ). Patients with low GCS scores at the time of admission had significantly higher mRS scores ( $p<0.001$ ). The relationship between IHS scores and mRS was significant ( $p<0.05$ ) (Table II).

## DISCUSSION

In the cerebrovascular disease group, spontaneous intracerebral hematomas are one of the leading causes of disability. Determining preventable risk factors and estimating the likelihood of sequelae after diagnosis is critical both before and after the diagnosis. Herein, advanced age, hypertension, anti-coagulant–antiaggregant use, and low GCS scores at the time of admission may be associated with elevated mRS scores. Patient management can be planned according to risk factors and characteristics at the time of clinical presentation.

Previous studies reported a positive relationship between the male gender and ICH. In a study that looked at the risk factors of 129 patients who had spontaneous intracerebral hematoma, the number of male patients was 62 (3). In the study of Ariesen et al., the risk of hematoma incidence was found to be 1.35 times higher in the male gender (1). Previous research has found that the male gender is a significant risk factor for spontaneous intracerebral hematoma (2,11,27,28), similar to our results. However, no significant relationship between mRS at discharge and gender was found in our study. Thus, no significant correlation was detected between the progressive course of the disease and the high rate of sequelae and male gender.

The risk of ICH increases with age, and this risk doubles every passing decade (27); the most important irreversible risk factor (1,11,27). Herein, the mean age of the patients is 59.8 years.

**Table I:** Demographic Characteristics of Patients Who Had Intracerebral Hematomas

| Variables                               | Primary intracerebral<br>hematoma, n (%) | Secondary intracerebral<br>hematoma, n (%) | Total |
|-----------------------------------------|------------------------------------------|--------------------------------------------|-------|
| <b>Age (years)</b>                      |                                          |                                            |       |
| <55                                     | 22 (61)                                  | 14 (39)                                    | 36    |
| 56-75                                   | 37 (75.5)                                | 12 (24.5)                                  | 49    |
| >76                                     | 25 (86.2)                                | 4 (13.8)                                   | 29    |
| <b>Gender</b>                           |                                          |                                            |       |
| Female                                  | 36 (68)                                  | 17 (32)                                    | 53    |
| Male                                    | 48 (78.6)                                | 13 (21.4)                                  | 61    |
| <b>Location</b>                         |                                          |                                            |       |
| Deep                                    | 26 (83.8)                                | 5 (16.2)                                   | 31    |
| Lobar                                   | 58 (69.8)                                | 25 (30.2)                                  | 83    |
| <b>Glasgow Coma Scale Score</b>         |                                          |                                            |       |
| <5                                      | 4 (66.6)                                 | 2 (33.4)                                   | 6     |
| 5-8                                     | 19 (82.6)                                | 4 (17.4)                                   | 23    |
| 9-12                                    | 33 (86.8)                                | 5 (13.2)                                   | 38    |
| >12                                     | 28 (59.5)                                | 19 (40.5)                                  | 47    |
| <b>Surgery</b>                          |                                          |                                            |       |
| No                                      | 40 (80)                                  | 10 (20)                                    | 50    |
| Yes                                     | 51 (69.8)                                | 22 (30.2)                                  | 73    |
| <b>Midline shift</b>                    |                                          |                                            |       |
| None                                    | 13 (81.2)                                | 3 (18.8)                                   | 16    |
| <4 mm                                   | 32 (66.6)                                | 16 (33.4)                                  | 48    |
| >4 mm                                   | 51 (78.5)                                | 14 (21.5)                                  | 65    |
| <b>Hematoma volume (cm<sup>3</sup>)</b> |                                          |                                            |       |
| <30                                     | 37 (67.3)                                | 18 (32.7)                                  | 55    |
| 30-50                                   | 21 (72.5)                                | 8 (27.5)                                   | 29    |
| >50                                     | 38 (84.5)                                | 7 (15.5)                                   | 45    |
| <b>IHS score</b>                        |                                          |                                            |       |
| 0                                       | 11 (47.8)                                | 12 (52.2)                                  | 23    |
| 1                                       | 31 (77.5)                                | 9 (22.5)                                   | 40    |
| 2                                       | 37 (80.5)                                | 9 (19.5)                                   | 46    |
| 3                                       | 14 (82.4)                                | 3 (17.6)                                   | 17    |
| 4                                       | 3 (100)                                  | 0                                          | 3     |
| <b>mRS</b>                              |                                          |                                            |       |
| 0                                       | 2 (20)                                   | 8 (80)                                     | 10    |
| 1                                       | 12 (52.2)                                | 11 (47.8)                                  | 23    |
| 2                                       | 10 (76.9)                                | 3 (23.1)                                   | 13    |
| 3                                       | 8 (80)                                   | 2 (20)                                     | 10    |
| 4                                       | 11 (100)                                 | 0                                          | 11    |
| 5                                       | 8 (88.8)                                 | 1 (11.2)                                   | 9     |
| 6                                       | 33 (86.8)                                | 5 (13.2)                                   | 38    |

**IHS:** Intracerebral hemorrhage score, **mRS:** Modified rankin score.

**Table II:** Relation with mRS in Intracerebral Hematoma Patients

| Variables                          | mRS |    |    |    |   |   |    | Total, n | p-value |
|------------------------------------|-----|----|----|----|---|---|----|----------|---------|
|                                    | 0   | 1  | 2  | 3  | 4 | 5 | 6  |          |         |
| Age, n (years)                     |     |    |    |    |   |   |    |          |         |
| <55                                | 5   | 10 | 8  | 2  | 0 | 1 | 10 | 36       | p=0.01  |
| 56-75                              | 4   | 11 | 3  | 6  | 7 | 4 | 14 | 49       |         |
| >76                                | 1   | 2  | 2  | 2  | 4 | 4 | 14 | 29       |         |
| Gender, n                          |     |    |    |    |   |   |    |          |         |
| Female                             | 5   | 12 | 4  | 5  | 4 | 6 | 17 | 53       | p=714   |
| Male                               | 5   | 11 | 9  | 5  | 7 | 3 | 21 | 61       |         |
| Hypertension, n                    |     |    |    |    |   |   |    |          |         |
| No                                 | 7   | 21 | 6  | 10 | 5 | 3 | 22 | 74       | p=0.01  |
| Yes                                | 3   | 2  | 7  | 0  | 6 | 6 | 16 | 40       |         |
| Anticoagulant-antiaggregant use, n |     |    |    |    |   |   |    |          |         |
| No                                 | 9   | 20 | 11 | 5  | 5 | 2 | 18 | 70       | p<0.001 |
| Yes                                | 1   | 3  | 2  | 5  | 6 | 7 | 20 | 44       |         |
| Glasgow Coma Scale Score, n        |     |    |    |    |   |   |    |          |         |
| <5                                 | 0   | 0  | 0  | 0  | 0 | 0 | 6  | 6        | p<0.001 |
| 5-8                                | 0   | 1  | 1  | 2  | 4 | 2 | 13 | 23       |         |
| 9-12                               | 0   | 6  | 5  | 6  | 5 | 5 | 11 | 38       |         |
| >12                                | 10  | 16 | 7  | 2  | 2 | 2 | 8  | 47       |         |
| Surgery, n                         |     |    |    |    |   |   |    |          |         |
| No                                 | 5   | 13 | 5  | 3  | 2 | 1 | 12 | 41       | p=0.3   |
| Yes                                | 5   | 10 | 8  | 7  | 8 | 7 | 23 | 68       |         |
| Midline shift, n                   |     |    |    |    |   |   |    |          |         |
| None                               | 0   | 0  | 0  | 0  | 1 | 0 | 0  | 1        | p<0.05  |
| <4 mm                              | 8   | 13 | 6  | 2  | 4 | 2 | 13 | 48       |         |
| >4 mm                              | 2   | 10 | 7  | 8  | 6 | 7 | 25 | 65       |         |
| IHS, n                             |     |    |    |    |   |   |    |          |         |
| 0                                  | 8   | 8  | 4  | 1  | 1 | 0 | 1  | 23       | p<0.05  |
| 1                                  | 2   | 12 | 2  | 1  | 3 | 3 | 7  | 30       |         |
| 2                                  | 0   | 1  | 6  | 6  | 6 | 4 | 19 | 42       |         |
| 3                                  | 0   | 2  | 1  | 2  | 1 | 2 | 9  | 17       |         |
| 4                                  | 0   | 0  | 0  | 0  | 0 | 0 | 2  | 2        |         |
| Opening to ventricles, n           |     |    |    |    |   |   |    |          |         |
| No                                 | 10  | 21 | 12 | 6  | 4 | 6 | 17 | 76       | p<0.05  |
| Yes                                | 0   | 2  | 1  | 4  | 7 | 3 | 21 | 38       |         |

**IHS:** Intracerebral hemorrhage score, **mRS:** Modified rankin score.

The increased prevalence of HT and decreased flexibility of the vessel wall with increasing age, as well as the fact that it is more easily affected by the effects of HT, can explain why IH is seen more in advanced age. In the study of Jørgensen et al., examining the relationship between prognosis and age, advanced age was associated with poor prognosis (19). In a study that looked at risk factors based on the mortality status of patients with spontaneous intracerebral hematoma,

it was discovered that mortality over the age of 65 increased significantly (5). In the present study, it was detected that the rate of poor prognosis was higher especially in patients over 75 years of age.

Previous research has highlighted the significance of hypertension in the etiology of spontaneous ICH, and the importance of hypertension was reported in previous studies (1,30). A history of HT was present in 72%–81% of ICH patients (24).

**Table III:** Mortality Status of Patients Who Had Intracerebral Hematomas

|                                        | Death     | Survival  | Total | p-value |
|----------------------------------------|-----------|-----------|-------|---------|
| Age, n (%)                             |           |           |       |         |
| <55                                    | 11 (29.7) | 26 (70.3) | 37    | 0.13    |
| 55-75                                  | 13 (27)   | 35 (73)   | 48    |         |
| >75                                    | 14 (48.2) | 15 (51.8) | 29    |         |
| Gender, n (%)                          |           |           |       |         |
| Female                                 | 17 (32)   | 36 (68)   | 53    | 0.07    |
| Male                                   | 21 (34.5) | 40 (65.5) | 61    |         |
| Hypertension, n (%)                    |           |           |       |         |
| No                                     | 22 (29.7) | 52 (70.3) | 74    | 0.2     |
| Yes                                    | 16 (40)   | 24 (60)   | 40    |         |
| Anticoagulant-antiaggregant use, n (%) |           |           |       |         |
| No                                     | 18 (25.7) | 52 (74.3) | 70    | 0.029   |
| Yes                                    | 20 (45.5) | 24 (54.5) | 44    |         |
| Glasgow Coma Scale Score, n (%)        |           |           |       |         |
| <5                                     | 6 (100)   | 0         | 6     | 0.00003 |
| 5-8                                    | 13 (56.5) | 10 (43.5) | 23    |         |
| 9-12                                   | 11 (28.9) | 27 (71.1) | 38    |         |
| >12                                    | 8 (17)    | 39 (83)   | 47    |         |
| Surgery, n (%)                         |           |           |       |         |
| No                                     | 12 (29.3) | 29 (70.7) | 41    | 0.6     |
| Yes                                    | 23 (33.8) | 45 (66.2) | 68    |         |
| Midline shift, n (%)                   |           |           |       |         |
| None                                   | 0         | 1 (100)   | 1     | 0.38    |
| <4 mm                                  | 14 (29.2) | 34 (70.8) | 48    |         |
| >4 mm                                  | 24 (36.9) | 41 (63.1) | 65    |         |
| Hematoma volume, n (%)                 |           |           |       |         |
| <30                                    | 1 (14.2)  | 6 (85.8)  | 7     | 0.54    |
| 30-50                                  | 2 (33.3)  | 4 (66.7)  | 6     |         |
| >50                                    | 35 (34.6) | 66 (65.4) | 101   |         |

In the multicenter stroke study in Türkiye, 79.2% of risk factor in ICH in our country was HT (23). Herein, the rate of HT was 35% in patients. This was discovered to be low in comparison to the data in the literature. However, 70% of patients diagnosed with HT according to mRS had a poor prognosis. When the survivors and those who died were compared in terms of HT history, a significant effect of HT history on mortality was found in a study that examined the 1-year prognosis of patients who had spontaneous intracerebral hematoma (28).

Oral anticoagulants (OACs) are used to treat intracerebral hematomas at a rate of about 20%. When patients who had similar risk factors were compared, the risk of IH was found to be 7–10 times higher in patients receiving OAC (32). The use of oral anticoagulants increased the risk of death in univariate analysis in a study that looked at the factors affecting the 30-day mortality of 598 patients with intracerebral hemorrhage. The cumulative risk for mortality in this study increased as the

day progressed. In this prospective cohort study of patients with acute ICH, patients treated with antithrombotic agents had a more severe clinical picture and a higher in-hospital mortality rate compared to patients who did not receive antithrombotic therapy (14). In a large retrospective analysis of more than 140,000 patients with ICH, prior oral anticoagulant use was associated with increased in-hospital deaths (18). A retrospective cohort study of over 20,000 patients with intracerebral hemorrhage found that those who used oral anticoagulants during hospital follow-up had higher 30-day, 1-year, and 5-year mortality rates. Oral anticoagulant use was found to increase mortality 1.3 times in-hospital follow-up and 1.18 times in 1-year mortality in multivariate and cox regression analyses (12). In the current study, 33 of 44 patients who used anticoagulants had a worse prognosis than mRS, whereas 45 of 70 patients who did not use OAC had a better prognosis.

Opening of bleeding to the intraventricular area causes poor prognosis and increased mortality rates (4,6,8,10,17,29). The development of obstructive hydrocephalus or compression of the ventricular blood on the periventricular structures may be the cause of the high mortality. Herein, the relationship between the opening of the hematoma to the ventricles and high Rankin scores in those with hematoma was found to be significant. Poor prognosis was detected in 31 of 38 patients who had bleeding into the ventricle. Tekinarslan et al. found that opening to the ventricle was associated with a poor prognosis in their study of patients with intracerebral hematomas, and 70.2% of the patients were in the poor prognosis group (28). Another factor that affects mortality is midline shift (20). In the study of Celikbilek et al., mortality was observed in 59.1% of those who had a shift and 17.7% of those who had no shifts (5). In a series of 141 patients, the presence of shift was found in 83.9% (6). Herein, the relationship between shifts and poor prognosis was significant.

The volume of bleeding is the most important factor influencing mortality (4,6,15). In patients who had hematoma volume  $>60 \text{ cm}^3$ , if the patient's GCS was  $<8$ , the 30-day mortality rate was 91%. The 30-day mortality rate in patients with GCS  $>9$  and hematoma volume of  $<30 \text{ cm}^3$  was 19%. It was detected that for every  $1 \text{ cm}^3$  increase in the initial hematoma volume, mortality increased by 1% (8). The size and location of the parenchymal hematoma are two important factors in the prognosis of spontaneous intracerebral parenchymal hematomas (22,31). Bleeding greater than 30 ml is associated with a poor prognosis. In those with bleeding greater than 60 ml and GCS 8, the expected mortality rate within 30 days is greater than 90% (31). Herein, 38 of 114 patients died and 33 (92.1%) of these patients had a bleeding volume  $>50 \text{ cm}^3$ .

Many studies found that advanced age, low GCS at presentation, hematoma volume, hematoma opening into the intraventricular or subarachnoid space, and midline shift were risk factors for poor prognosis (13). When we looked at our series, we found that low GCS at the time of presentation, high hematoma volume, and high midline shift were all directly proportional to elevated mRS and were reported as poor prognostic factors, just like those in other studies.

There were some limitations in the present study. Some of them are as following: the data came from a single source; the population of the study was small; and since it had a retrospective design, comorbidities other than hypertension could not be evaluated.

## CONCLUSION

Spontaneous intracerebral hematomas are among the leading causes of disability in many countries. The detection and treatment of underlying diseases in people with preventable risk factors are important in terms of preventing the formation of intracerebral hematomas. Society's awareness of risk factors should be prioritized for early diagnosis and treatment to reduce disability rates. Further research on this topic is needed, with a larger number of patient groups and more detailed examinations of risk factors.

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### AUTHORSHIP CONTRIBUTION

Study conception and design: SC

Data collection: SC

Analysis and interpretation of results: YE, HC, AT

Draft manuscript preparation: SC, HK

Critical revision of the article: MAB

Other (study supervision, fundings, materials, etc...): AK, MEY, BA, ZCG

All authors (SC, YE, HC, AT, HK, AK, MEY, BA, ZCG, MAB) reviewed the results and approved the final version of the manuscript.

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