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SCIENTIFIC ARTICLE

# Risk factors for mortality after subarachnoid hemorrhage: a retrospective observational study

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**KEYWORDS**
Intensive Care Unit;
Inter-hospital transfer;
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Carbapenemase-producing bacteria;
Hypernatraemia

**Abstract**
*Background and objectives:* Subarachnoid hemorrhage is an important cause of morbidity and mortality. The aim of the study was to determine predictors of mortality among patients with subarachnoid hemorrhage hospitalized in an Intensive Care Unit.
*Methods:* This is a retrospective study of patients with subarachnoid hemorrhage admitted to the Intensive Care Unit of our institution during a 7 year period (2009-2015). Data were collected from the Intensive Care Unit computerized database and the patients' chart reviews.
*Results:* We included in the study 107 patients with subarachnoid hemorrhage. A ruptured aneurysm was the cause of subarachnoid hemorrhage in 76 (71%) patients. The overall mortality was 40% (43 patients), and was significantly associated with septic shock, midline shift on CT scan, inter-hospital transfer, aspiration pneumonia and hypernatraemia during the first 72 hours of Intensive Care Unit stay. Multivariate analysis of patients with subarachnoid hemorrhage following an aneurysm rupture revealed that mortality was significantly associated with septic shock and hypernatremia during the first 72 hours of Intensive Care Unit stay, while early treatment of aneurysm (clipping or endovascular coiling) within the first 72 hours was identified as a predictor of a good prognosis.
*Conclusions:* Transferred patients with subarachnoid hemorrhage had lower survival rates. Septic shock and hypernatraemia were important complications among critically ill patients with subarachnoid hemorrhage and were associated increased mortality.


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**PALAVRAS-CHAVE**
Unidade de Tratamento Intensivo;
Transferência inter-hospitalar;
Choque séptico;
Bactérias produtoras de carbapenemases;
Hipernatremia

**Fatores de risco para mortalidade após hemorragia subaracnoidea: estudo observacional retrospectivo**

**Resumo**
*Justificativa e objetivos:* A hemorragia subaracnoidea é uma causa importante de morbidade e mortalidade. O objetivo do estudo foi determinar os preditivos de mortalidade entre os pacientes com hemorragia subaracnoidea internados em uma Unidade de Terapia Intensiva.
*Métodos:* Estudo retrospectivo de pacientes com hemorragia subaracnoidea internados na Unidade de Terapia Intensiva de nossa instituição de 2009 a 2015. Os dados foram coletados do banco de dados eletrônico da Unidade de Terapia Intensiva e de revisões dos prontuários dos pacientes.
*Resultados:* Incluímos no estudo 107 pacientes com hemorragia subaracnoidea. A ruptura de aneurisma foi a causa da hemorragia subaracnoidea em 76 pacientes (71%). A mortalidade geral foi de 40% (43 pacientes) e esteve significativamente associada ao choque séptico, desvio da linha média na tomografia computadorizada, transferência inter-hospitalar, pneumonia por aspiração e hipernatremia durante as primeiras 72 horas de internação na Unidade de Terapia Intensiva. A análise multivariada dos pacientes com hemorragia subaracnoidea pós-ruptura de aneurisma revelou que a mortalidade esteve significativamente associada ao choque séptico e hipernatremia nas primeiras 72 horas de permanência na Unidade de Terapia Intensiva, enquanto o tratamento precoce do aneurisma (clipagem ou embolização endovascular) nas primeiras 72 horas foi identificado como preditivo de um bom prognóstico.
*Conclusões:* Os pacientes com hemorragia subaracnoidea que foram transferidos apresentaram taxas menores de sobrevivência. Choque séptico e hipernatremia foram complicações importantes entre os pacientes gravemente enfermos com hemorragia subaracnoidea e foram associados ao aumento da mortalidade.


## Introduction

SAH is a severe and complex disease which must be managed in specialized centers. Despite recent advances in treatment of SAH, either surgically or by endovascular techniques, it remains an important cause of morbidity and mortality and it usually warrants admission to Intensive Care Unit (ICU). Based on several reports, the 30 day mortality is 18%–40%.[1,2]

Previous studies have shown that prompt and timely surgical intervention was associated with better survival, even in patients with poor prognosis.[3,4] Unfortunately, an important proportion of Greek population lives in rural areas or islands and since neurosurgical departments are situated in tertiary-university hospitals, these patients are less likely to timely reach centralized services, possibly resulting in worst outcome.[5]

Our study aimed to clarify the in-hospital mortality of patients with SAH hospitalized in a tertiary Greek ICU and to assess the role of inter-hospital transfer in survival.

## Material and methods

This single-center retrospective study was conducted in the general ICU (13 beds) of the University General Hospital of Patras (UGHP), Greece during a seven-year period (January 2009–December 2015). Our institution is the tertiary reference hospital for the region of Western Greece, Peloponnese and Ionian Islands, covering a population of approximately one million people. Ethical approval for this study was provided by the Research Ethics Committee of the UGHP (nº 571).

All adult patients (age >18 years) with SAH who were admitted to the ICU during the study period were included in the study. Data were retrospectively collected from the ICU's computerized database (Criticus™, University of Patras) and patients' chart reviews. All patients were mechanically ventilated upon admission. According to severity scores, APACHE II (Acute Physiology and Chronic Health Evaluation II score), SAPS II (Simplified Acute Physiology Score II), SOFA (Sequential Organ Failure Assessment) scores, Glasgow Comas Scale (GCS), World Federation of Neurological Surgeons (WFNS) and Hunt & Hess (H&H) grades were assessed upon ICU admission for each patient.[6–9] Infections were categorized as sepsis or septic shock according to definition proposed by the Third International Consensus.[10] In case of increased intracranial pressure, an External Ventricular Drain (EVD) was placed with or without decompressive craniotomy and hematoma evacuation. In cases of aneurysmal SAH, treatment included clipping or endovascular coiling. Decision on treatment modality was based on an interdisciplinary consensus in each individual case after review of medical records, clinical manifestations, comorbidities, severity scores and CT findings.

Statistical analysis was performed with SPSS version 23.0 (IBM, SPSS, Chicago, IL) software. Categorical variables were

**Table 1** Univariate and multivariate analyses of predictors of morality of all patients with subarachnoid hemorrhage admitted in ICU.

| Characteristics | Univariate analysis | | | Multivariate analysis | |
|---|---|---|---|---|---|
| | Survivors ($n = 62$) | Non-survivors ($n = 45$) | $p$ | $p$ | OR (95% CI) |
| Demographics | | | | | |
| Age (years) | $60 \pm 11$ | $58 \pm 12$ | 0.835 | | |
| Male gender | 26 (42) | 29 (64) | 0.031 | – | – |
| Emergency department | | | | | |
| Syncope | 10 (16) | 10 (22) | 0.459 | | |
| Confusion | 30 (48) | 37 (82) | 0.001 | – | – |
| Coma | 9 (15) | 20 (44) | 0.001 | – | – |
| Epilepsy | 1 (2) | 2 (4) | 0.571 | | |
| Anisocoria | 3 (5) | 9 (20) | 0.026 | – | – |
| CT scan findings | | | | | |
| Intraventricular hemorrhage | 12 (19) | 14 (31) | 0.178 | | |
| Intraparenchymal hemorrhage | 17 (27) | 19 (42) | 0.147 | | |
| Brain edema | 12 (19) | 12 (27) | 0.482 | | |
| Midline shift | 11 (18) | 18 (40) | 0.015 | 0.036 | 3.8 (1.1–12.9) |
| Hydrocephalus | 11 (18) | 14 (31) | 0.164 | | |
| Aneurysm | 47 (76) | 29 (64) | 0.280 | | |
| ICU admission | | | | | |
| Transfer from other hospital | 29 (47) | 31 (69) | 0.030 | 0.008 | 5.1 (1.5–17.0) |
| Distance from UGHP (km) | $42 \pm 53$ | $66 \pm 76$ | 0.047 | – | – |
| Aspiration pneumonia upon admission | 1 (2) | 11 (24) | < 0.001 | 0.031 | 21.2 (1.3–340.1) |
| GCS upon presentation | $12 \pm 3$ | $9 \pm 4$ | < 0.001 | – | – |
| GCS upon intubation | $9 \pm 4$ | $6 \pm 2$ | < 0.001 | – | – |
| Hunt & Hess grade $\geq 4$ | 16 (26) | 32 (71) | < 0.001 | – | – |
| WFNS grade $\geq 4$ | 39 (63) | 43 (96) | < 0.001 | – | – |
| APACHE II Score upon admission | $16 \pm 57$ | $19 \pm 3$ | 0.023 | | |
| SAPS II Score upon admission | $36 \pm 9$ | $40 \pm 7$ | 0.054 | – | – |
| SOFA Score upon admission | $7 \pm 3$ | $8 \pm 2$ | 0.001 | | |
| External ventricular drain | 39 (63) | 24 (53) | 0.329 | | |
| Decompressive craniotomy | 17 (27) | 8 (18) | 0.355 | | |
| Hospitalization data | | | | | |
| ICU length of stay (days) | $12 \pm 10$ | $18 \pm 22$ | 0.078 | | |
| Vasopressors | 25 (40) | 35 (78) | <0.001 | – | – |
| Septic shock | 7 (11) | 19 (42) | <0.001 | <0.001 | 20.7 (5.0–85.8) |
| Carbapenemase-producing gram-negative bacteremia | 10 (16) | 16 (36) | 0.024 | – | – |
| Hypernatremia during the first 72 hours | 5 (8) | 21 (47) | <0.001 | <0.001 | 22.1 (4.6–105.5) |

Data are number (%) of patients or mean ± SD.

analyzed by using the Fisher exact test and continuous variables with Mann–Whitney *U*-test, as appropriate. All backward stepwise multiple logistic regression analysis used all those variables from the univariate analysis with a $p < 0.1$. Factors contributing to multicollinearity were excluded from the multivariate analysis. Mortality rates according to distance of transfer were assessed using Spearman's correlation analysis. The accuracy of different predicting scores upon intubation to predict mortality was assessed using receiver operating characteristic analysis. All statistic tests were 2 tailed and $p < 0.05$ was considered statistically significant.

## Results

Of the 107 SAH cases, 76 (71%) were due to aneurysm rupture. Overall mortality was 40% (43 patients). Univariate and multivariate analyses for predictors of mortality of all SAH patients are shown in Table 1. Comorbidities did not influence mortality. Mortality among all SAH patients was significantly associated with septic shock ($p < 0.001$; OR = 20.7; 95% CI 5.0–85.8), midline shift on CT scan ($p = 0.036$; OR = 3.8; 95% CI 1.1–12.9), inter-hospital transfer ($p = 0.008$; OR = 5.1; 95% CI 1.5–17.0), aspiration pneumonia upon admission ($p = 0.031$; OR = 21.2; 95% CI 1.3–340.1) and

**Table 2** Univariate and multivariate analyses of predictors of morality of patients with aneurysmal subarachnoid hemorrhage admitted in ICU.

| Characteristics | Univariate analysis | | | Multivariate analysis | |
|---|---|---|---|---|---|
| | Survivors ($n=47$) | Non-survivors ($n=29$) | $p$ | $p$ | OR (95% CI) |
| Demographics | | | | | |
| Age (years) | 57 ± 10 | 59 ± 10 | 0.535 | | |
| Male gender | 20 (43) | 16 (55) | 0.347 | | |
| Emergency department | | | | | |
| Syncope | 9 (19) | 6 (21) | 1.000 | | |
| Confusion | 20 (43) | 23 (79) | 0.002 | – | – |
| Coma | 6 (13) | 12 (41) | 0.006 | – | – |
| Epilepsy | 1 (2) | 2 (7) | 0.554 | | |
| Anisocoria | 2 (4) | 6 (21) | 0.048 | – | – |
| CT scan findings | | | | | |
| Intraventricular hemorrhage | 8 (17) | 10 (35) | 0.101 | | |
| Intraparenchymal hemorrhage | 10 (21) | 8 (28) | 0.585 | | |
| Brain edema | 5 (11) | 7 (24) | 0.194 | | |
| Midline shift | 4 (9) | 10 (35) | 0.007 | – | – |
| Hydrocephalus | 9 (19) | 8 (28) | 0.410 | | |
| Aneurysm | – | – | – | | |
| ICU admission | | | | | |
| Transfer from other hospital | 21 (45) | 20 (69) | 0.058 | – | – |
| Distance from UGHP (km) | 37 ± 46 | 64 ± 92 | 0.147 | – | – |
| Aspiration pneumonia upon admission | 1 (2) | 5 (17) | 0.028 | – | – |
| GCS upon presentation | 12 ± 3 | 10 ± 4 | 0.002 | | |
| GCS upon intubation | 10 ± 4 | 7 ± 3 | 0.001 | – | – |
| Hunt & Hess grade ≥ 4 | 10 (21) | 20 (69) | <0.001 | – | – |
| WFNS grade ≥ 4 | 27 (57) | 27 (93) | 0.001 | – | – |
| APACHE II score upon admission | 15 ± 6 | 19 ± 4 | 0.040 | | |
| SAPS II score upon admission | 35 ± 10 | 39 ± 8 | 0.088 | – | – |
| SOFA score upon admission | 6 ± 3 | 8 ± 2 | 0.003 | | |
| External ventricular drain | 28 (60) | 18 (62) | 1.000 | | |
| Decompressive craniotomy | 10 (21) | 6 (21) | 1.000 | | |
| Aneurysm embolism | 22 (47) | 10 (35) | 0.344 | | |
| Aneurysm clipping | 18 (38) | 5 (17) | 0.072 | – | – |
| Timing of aneurysm treatment (days; clipping or embolism) | 1 ± 2 | 3 ± 3 | 0.003 | | |
| Ultra-early (<1 day) and early (1–3 days) | 38 (81) | 7 (24) | <0.001 | 0.002 | 0.019 (0.002–0.230) |
| Intermediate-late (>3 days) or no treatment | 9 (19) | 22 (76) | | | |
| Hospitalization data | | | | | |
| ICU length of stay (days) | 12 ± 10 | 25 ± 29 | 0.005 | | |
| Vasopressors | 18 (38) | 23 (79) | 0.001 | – | – |
| Septic shock | 4 (9) | 15 (52) | <0.001 | <0.001 | 156.9 (9.5–2586.8) |
| Carbapenemase-producing gram-negative bacteremia | 7 (15) | 12 (41) | 0.014 | – | – |
| Hypernatremia during the first 72 h | 4 (9) | 13 (45) | <0.001 | 0.013 | 23.8 (2.0–290.7) |

Data are number (%) of patients or mean ± SD.

hypernatraemia during the first 72 h of ICU stay ($p < 0.001$; OR = 22.1; 95% CI 4.6–105.5).

Univariate and multivariate analyses for predictors of mortality of patients with aneurysmal SAH ($n = 76$) are shown in Table 2. Multivariate analysis of patients with aneurysmal SAH revealed that mortality was significantly associated with septic shock ($p < 0.001$; OR = 156.9; 95% CI 9.5–2586.8) and hypernatraemia during the first 72 h of ICU stay ($p = 0.013$; OR = 23.8; 95% CI 2.0–290.7), while treatment of aneurysm (clipping or endovascular coiling) within

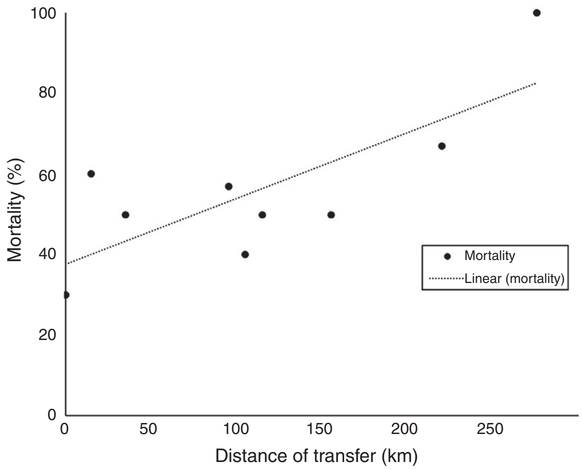


**Figure 1** Correlation between mortality rates and distance of transfer.

three days ($p = 0.002$; OR = 0.019; 95% CI 0.002–0.230) was identified as a predictor of a good prognosis.

Since transfer of patients was associated with increased mortality, an analysis of factors that differ among transferred patients ($n = 60$) and those who directly admitted ($n = 47$) to our ICU was performed (Table 3). Among the 60 transferred patients, 27 were intubated before their transfer, whereas 23 from the 33 patients, who were intubated in the UGHP, deteriorated their GCS during transfer and although an indication for intubation was met (GCS < 9) they were intubated upon arrival. Multivariate analysis revealed that ICU mortality ($p = 0.008$; OR = 4.3; 95% CI 1.5–12.5), GCS $\leq$7 upon intubation ($p = 0.010$; OR = 1.4; 95% CI 1.1–1.9) and WFNS grade $\geq$4 ($p = 0.001$; OR = 79.0; 95% CI 6.6–945.8) were associated with transfer of patients, while directly admitted patients had significantly higher rates of decompressive craniotomy ($p = 0.007$; OR = 0.156; 95% CI 0.041–0.599). Mortality rate progressively in proportion to the distance of transfer ($r = 0.586$; $p = 0.047$), as depicted in Fig. 1. The accuracy of APACHE II, SAPS II, SOFA scores, H&H and WFNS grades and GCS upon intubation in predicting mortality were 0.679, 0.617, 0.692, 0.791, 0.725 and 0.745, respectively.

## Discussion

In the present study, SAH accounted for 4% of all ICU admissions and the mortality of patients was 42%, higher than that reported from other studies.[1,2] It is important to acknowledge that there was a higher rate of patients with increased severity of disease as depicted by measured scores (45% of patients with H&H grade $\geq$4 and 77% with WFNS grade $\geq$4).

Another important factor that adversely influenced survival was inter-hospital transfer, as shown by multivariate analysis. There are conflicting results concerning the effect of transfer to specialized centers on mortality,[5] with most recent studies concluding that patients undergoing interhospital transfer had similar mortality rate as those that were directly admitted to a specialized center.[9,11] On the contrary, in our study, transferred patients had worse outcome (52% vs. 30%; $p = 0.030$). This difference was most likely due to the fact that our institution is the only tertiary university hospital in South-Western Greece receiving patients from regional hospitals within a distance up to 280 km. In a previous report, median transfer distance was 12 km (range 2–256 km), while in our cohort the median distance was 95 km (range 12–280 km).[12] In our study, mortality rate increased proportionately to the distance of interhospital transfer (Fig. 1). This transfer of critically ill patients significantly delayed prompt surgical interventions in combination of potentially instability of vital signs for a period of time. Even though transferred and non-transferred patients had no difference of GCS upon presentation, transferred patients had a worse neurological grade upon arrival at the emergency department, as depicted by the higher rates of coma and lower GCS grade upon intubation. Failure to intubate transferred patients led to higher percentages of aspiration pneumonia (17% vs. 4%; $p = 0.063$), which in turn was significantly associated with reduced survival.

Prompt and timely intervention (within the first three days from presentation) was independently associated with better outcome. Early intervention (clipping or endovascular coiling) was considered an option for all patients with SAH, even for those with low probability of survival. In the past, it was an option only for patients with better neurological grades. The effect of timely intervention on aneurysmal SAH outcome was shown in previous studies.[3,4] In a previous meta-analysis of poor-grade aneurysmal SAH, patients receiving ultra-early (within 48 h post ictus) treatment (surgical or endovascular) had better neurological outcome.[13] In our study, aneurysm embolism was the preferred approach for the treatment of aneurysmal SAH, although both techniques (surgical or endovascular) showed comparable efficacy.

When performance of severity scores upon admission was compared, H&H grade showed the higher accuracy in predicting ICU mortality in comparison with general severity scores (APACHE II, SAPS II, SOFA) or more specific grading scales (GCS and WFNS scale). Their accuracy in the present study might be lower than previously found, most likely due to the fact that a limited number of patients with good scores were admitted to the ICU.[14] As previously shown, since no score showed significant superiority on outcome prediction of SAH patients, all the aforementioned scores could be used to roughly predict outcome and guide clinicians.[6]

In line with previous studies, disorders of sodium concentration were frequent during the course of SAH with hypernatraemia associated with poor outcome.[15,16] In our study, hypernatraemia during the first 72 h of stay occurred in 24% of patients, comparable to previous studies (12%–22%), and was significantly associated with increased mortality in all SAH patients and in the subgroup of those with aneurysmal SAH.[16]

SAH is a common cause of Systemic Inflammatory Response Syndrome (SIRS), therefore it remains a clinical challenge to distinguish between SIRS from true infection. During their stay in ICU, 49 patients (46%) developed sepsis, while septic shock affected 26 of them (24%). These rates were higher from those previously reported.[17] Septic shock was an independent predictor of ICU mortality for all patients with SAH and for the subgroup of patients with aneurysmal SAH. In a previous study of spontaneous aneurysmal subarachnoid hemorrhage, sepsis

**Table 3** Univariate and multivariate analyses of differences among patients that were directly admitted as compared to transferred patients.

| Characteristics | Univariate analysis | | | Multivariate analysis | |
|---|---|---|---|---|---|
| | Direct admission ($n = 47$) | Transfer ($n = 60$) | $p$ | $p$ | OR (95% CI) |
| Demographics | | | | | |
| Age (years) | 58 ± 11 | 60 ± 11 | 0.264 | | |
| Male gender | 21 (45) | 34 (57) | 0.246 | | |
| Emergency department | | | | | |
| Syncope | 7 (15) | 13 (22) | 0.458 | | |
| Confusion | 22 (47) | 45 (75) | 0.005 | – | – |
| Coma | 9 (19) | 20 (33) | 0.127 | | |
| Epilepsy | 0 (0) | 3 (5) | 0.254 | | |
| Anisocoria | 7 (15) | 5 (8) | 0.360 | | |
| CT scan findings | | | | | |
| Intraventricular hemorrhage | 8 (17) | 18 (30) | 0.173 | | |
| Intraparenchymal hemorrhage | 14 (30) | 22 (37) | 0.538 | | |
| Brain edema | 9 (19) | 15 (25) | 0.495 | | |
| Midline shift | 10 (21) | 19 (32) | 0.277 | | |
| Hydrocephalus | 8 (17) | 17 (28) | 0.250 | | |
| Aneurysm | 36 (77) | 40 (67) | 0.290 | | |
| ICU admission | | | | | |
| Aspiration pneumonia upon admission | 2 (4) | 10 (17) | 0.063 | – | – |
| GCS upon presentation | 11 ± 4 | 11 ± 4 | 0.434 | | |
| GCS upon intubation | 10 ± 4 | 7 ± 3 | 0.011 | 0.010 | 1.4 (1.1–1.9) |
| Hunt & Hess grade ≥ 4 | 14 (30) | 34 (57) | 0.006 | – | – |
| WFNS grade ≥ 4 | 26 (55) | 56 (93) | <0.001 | 0.001 | 79.0 (6.6–945.8) |
| APACHE II score upon admission | 17 ± 6 | 17 ± 4 | 0.417 | | |
| SAPS II score upon admission | 37 ± 9 | 38 ± 9 | 0.665 | | |
| SOFA score upon admission | 7 ± 3 | 8 ± 2 | 0.219 | | |
| External ventricular drain | 31 (66) | 32 (53) | 0.236 | | |
| Decompressive craniotomy | 17 (36) | 8 (13) | 0.010 | 0.007 | 0.156 (0.041–0.599) |
| Early (<3 days) aneurysm treatment | 28 (60) | 17 (28) | 0.002 | – | – |
| Hospitalization data | | | | | |
| Mortality | 14 (30) | 31 (52) | 0.030 | 0.008 | 4.3 (1.5–12.5) |
| ICU length of stay (days) | 13 ± 13 | 19 ± 24 | 0.193 | | |
| Vasopressors | 22 (47) | 38 (63) | 0.117 | | |
| Septic shock | 13 (28) | 13 (22) | 0.503 | | |
| Carbapenemase–producing gram-negative bacteremia | 9 (19) | 17 (28) | 0.364 | | |
| Hypernatremia during the first 72 h | 11 (23) | 15 (25) | 1.000 | | |

Data are number (%) of patients or mean ± SD.

was associated with higher mortality.[18] The main concern in Greek ICUs is that most of these infections are provoked by carbapenem-resistant gram negative bacteria (26 patients; 53%), which were associated with high mortality rates due to our limited antimicrobial options.[19] Since carbapenemase-producing gram negative bacteria have disseminated worlwide, they pose an immediate threat to most critically ill patients globally.

There were several limitations that must be taken in consideration. First, this was a single center study with a relative small number of patients. Second, even though the distance among hospitals was included, time of transferring was not measured. This could constitute a bias since the infrastructure vary among different areas of west Greece and patients arriving in hospitals on islands were transferred to UGHP by sea or air transport, which could significantly influence transfer time.

## Conclusions

SAH is an important cause of ICU admission associated with increased mortality. Severity scores such as GCS, WFNS and Hunt and Hess scales remain important tools in predicting survival and guiding clinicians. Septic shock due to carbapenem-resistant bacteria constitutes an important complication among Greek critically ill patients with SAH and was found to be independently associated with reduced survival. Since transferred patients from other hospitals, as compared to patients arriving directly at our institution had lower survival rates, a reorganization of our transfer system may be warranted in order to reduce the time between first presentation and arrival to the specialized center.

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## Conflicts of interest

The authors declare no conflicts of interest.

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