ORIGINAL ARTICLE

Comorbidities and Medical Complications in Hospitalized Subarachnoid Hemorrhage Patients

Solon Schur, Dimitra Panagiotoglou, Salvatore Di Maio, David Buckeridge

Abstract: ***Background:*** Aneurysmal subarachnoid hemorrhage (SAH) remains a devastating condition with a case fatality of 36% at 30 days. Risk factors for mortality in SAH patients include patient demographics and the severity of the neurological injury. Pre-existing conditions and non-neurological medical complications occurring during the index hospitalization are also risk factors for mortality in SAH. The magnitude of the effect on mortality of pre-existing conditions and medical complications, however, is less well understood. In this study, we aim to determine the effect of pre-existing conditions and medical complications on SAH mortality. ***Methods:*** For a 25% random sample of the Greater Montreal Region, we used discharge abstracts, physician billings, and death certificate records, to identify adult patients with a new diagnosis of non-traumatic SAH who underwent cerebral angiography or surgical clipping of an aneurysm between 1997 and 2014. ***Results:*** The one-year mortality rate was 14.76% (94/637). Having ≥3 pre-existing conditions was associated with increased one-year mortality OR 3.74, 95% CI [1.25, 9.57]. Having 2, or ≥3 medical complications was associated with increased one-year mortality OR, 2.42 [95% CI 1.25–4.69] and OR, 2.69 [95% CI 1.43–5.07], respectively. Sepsis, respiratory failure, and cardiac arrhythmias were associated with increased one-year mortality. Having 1, 2, or ≥3 pre-existing conditions was associated with increased odds of having medical complications in hospital. ***Conclusions:*** Pre-existing conditions and in-hospital non-neurological medical complications are associated with increased one-year mortality in SAH. Pre-existing conditions are associated with increased medical complications.

RÉSUMÉ : Comorbidités et complications médicales dans le cas de patients hospitalisés à la suite d'une hémorragie sous-arachnoïdienne. ***Contexte*** **:** Les hémorragies sous-arachnoïdiennes (HSA) en cas de rupture d'anévrisme continuent à représenter une condition médicale accablante avec un taux de mortalité de 36 % au bout du trentième jour. Les facteurs de risque de mortalité chez les patients atteints de HSA en cas de rupture d'anévrisme comprennent leurs caractéristiques démographiques ainsi que la gravité des lésions neurologiques survenues. Qui plus est, des conditions préexistantes et des complications médicales non neurologiques survenant au cours de l'hospitalisation initiale sont également des facteurs de risque chez ces patients. Cela dit, l'ampleur des effets des conditions préexistantes et des complications médicales sur leur taux de mortalité demeure toutefois moins bien comprise. Notre but dans cette étude est ainsi de déterminer la nature de ces effets. ***Méthodes*** **:** C'est à partir d'un échantillon aléatoire de 25 % de la région du Grand Montréal et à l'aide de registres de congés, de factures de médecins et de certificats de décès que nous avons pu identifier des patients adultes chez qui un nouveau diagnostic non-traumatique de HSA en cas de rupture d'anévrisme avait été posé entre 1997 et 2014 et qui avaient bénéficié d'une angiographie cérébrale ou d'un clippage chirurgical. ***Résultats*** **:** Le taux de mortalité de ces patients s'est élevé à 14,76 % (94/637) au bout d'un an. Le fait d'avoir 3 conditions préexistantes ou plus a été associé à un taux de mortalité plus élevé (RC 3,74 ; IC 95 % [1,25 ; 9,57]. De plus, le fait d'avoir 2 ou 3 complications médicales ou plus a aussi été associé à un taux de mortalité plus élevé (respectivement RC 2,42 [IC 95 % ; 1,25 – 4,69] et RC 2,69 [IC 95 % ; 1,43 – 5,07]). Tant le sepsis, l'insuffisance respiratoire que les arythmies cardiaques ont été associées à une augmentation de la mortalité au bout d'un an. Finalement, le fait d'avoir 1, 2 ou 3 conditions préexistantes ou plus a été associé à une probabilité accrue d'avoir des complications médicales à l'hôpital. ***Conclusion*** **:** En somme, les conditions préexistantes et les complications médicales non neurologiques au moment d'une hospitalisation sont associées à une augmentation de la mortalité au bout d'un an dans des cas de HSA attribuables à une rupture d'anévrisme tandis que les conditions préexistantes sont associées à une augmentation des complications médicales.

Key words: Subarachnoid hemorrhage, Pre-existing conditions, Medical complications, Mortality, Angiography, Aneurysm clipping

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Introduction

Subarachnoid hemorrhages (SAHs) represent 5%–10% of all strokes[1,2] and are usually caused by cerebral artery aneurysm rupture.[3,4] In Canada, the incident admissions for SAH are estimated to be 6.3 per 100 000 person years. For patients deemed salvageable at the time of presentation, the major goal of treatment is to avoid rebleeding by rapidly securing the aneurysm via neurosurgical clipping or angiography. Despite improvements in mortality over the past decade, SAH remains a devastating condition with a case-fatality ratio approaching

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36%.[5] In view of this persistent high mortality, a large body of research has sought to identifying risk factors for mortality in SAH.

Age[6–10] and the severity of neurological injury[11,12] are well established risk factors for mortality. There is also mounting evidence that pre-existing conditions, including hypertension, cardiac disease, cerebrovascular disease, and renal disease, increase mortality in SAH.[13,14] Non-neurological medical complications occurring during the initial admission also seem to play an important role in SAH mortality.[9,15] For both pre-existing conditions and medical complications however, the extent to which they contribute to mortality and which specific diagnoses matter most remains unclear. In this study, our goal was to assess the effect of pre-existing conditions and medical complications on mortality, at a population level using administrative health data.

Methods

Data Set Source

Administrative health data from the Population Health Record (PopHR) database were used. The PopHR database includes health records for a 25% random sample (open cohort) of the population from the Census Metropolitan Area of Montréal, Canada.[16] It uses data from the single payer public health insurance, the Régie de l'Assurance Maladie du Québec (RAMQ), which covers over 97% of the Quebec population,[17] along with death certificates and the discharge abstract data from the Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (MED-ECHO) database. The information from those three databases was linked by patient deidentified indicators. The study period spanned from 1997 to 2014.

Study Population

Inclusion criteria: Patients were selected based on the documented primary International Classification of Diseases, 9th Revision (ICD-9) diagnosis code of SAH (430); or ICD-10 diagnosis code of SAH (I600-9). Both the MED-ECHO discharge abstract database and RAMQ billings were queried. The Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CPP) codes and Canadian Classification of Health Interventions (CCI) codes for surgical clipping and diagnostic and therapeutic angiography were retained to select patients having undergone these procedures (see Appendix 1 under "retained endovascular and neurosurgical procedures" for the full list of procedures and procedure codes). The ICD-9 and CPP codes were used until March 2006, after which the database only includes ICD-10 and CCI codes. We selected in this study only the initial hospitalization episodes (referred to as the index hospitalization) where patients were given the diagnosis of SAH. The initial hospitalization episode included all hospital stays within 3 days of the earliest admission with SAH diagnosis (to include nested admissions, early transfers, and hospital stays where patients may not have been given the diagnosis of SAH), and the subsequent transfers to other institutions. A hospital stay was considered as a transfer, and part of the same hospitalization episode if the patient was admitted within one day of the date of discharge of the previous hospitalization. The positive predictive value (PPV) of using this time interval was found to be 86.4% in a study using administrative health data from the Alberta discharge abstract database.[18] While the PPV is higher for shorter time intervals (96% for a 6-hour interval), the sensitivity is highest for the larger time interval (98.7%). As the admission and discharge times are not available in our database, and to increase the sensitivity, we opted to use a time interval of less than or equal to one day from the time of discharge[18] to define our hospitalization episode.

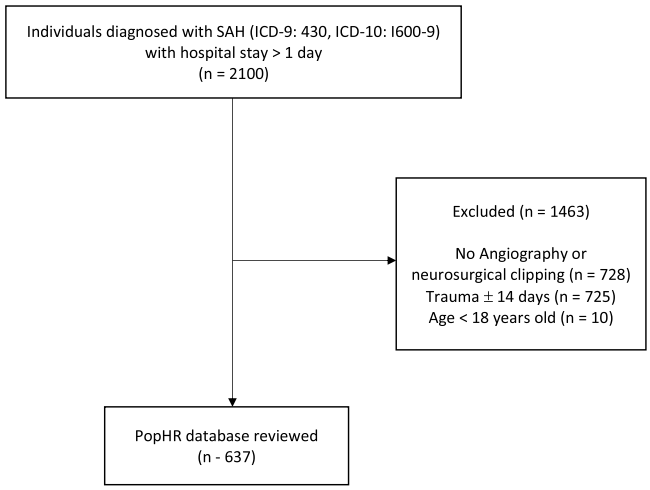

Figure 1: *The Population Health Records database was used to identify 637 adult patients with subarachnoid hemorrhage diagnostic codes, who underwent angiography or neurosurgical clipping of an aneurysm. Patients with concomitant trauma codes were excluded.*

Exclusion criteria: Patients <18 years old were excluded. Patients who were not covered by the RAMQ were not included in this study. Patients not covered by the RAMQ include patients from other provinces covered by their own provincial insurance programs, patients with private insurance visiting Quebec, or patients covered by the Interim Federal Health Program if they are refugees, or from specific groups.[17,19] Patients who did not undergo neurosurgical clipping of an aneurysm or angiography were also excluded. Patients with trauma codes (see Appendix 1, under "trauma codes" for full list of distinct trauma ICD codes used), documented within 14 days of the initial diagnosis of SAH, were excluded, including if the trauma codes were documented during the index hospitalization. We included the cut-off of 14 days prior and after the initial SAH diagnosis because it takes up to 10–14 days for SAH blood to get reabsorbed on imaging,[20] and the length of stay for traumatic brain injury is usually <14 days.[21] See Figure 1 for the flow diagram of the study cohort selection.

Identifying Pre-Existing Conditions

To find pre-existing conditions, the MED-ECHO and RAMQ billing databases were queried for all ICD-9 and ICD-10 codes documented for the patients in our cohort the year prior to the index hospitalization for SAH.[18] The pre-existing conditions considered for analysis were those deemed severe, as per the Charlson comorbidity index.[13,14] Dyslipidemia and hypertension were added to the list as they were identified as potential risk factors for SAH mortality in previous studies.[9,10,13] The full list of pre-existing conditions considered included: dyslipidemia, hypertension, congestive heart failure, myocardial infarction,

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Table 1: Multivariate logistic regression for one-year mortality

Variable	Mean	OR	95%CI	*p* value
Age (in years), mean (SD)	54.63 (13.71)	1.00	0.99, 1.02	0.796
Sex, n (%)				
Male	228 (35.79%)	1.45	0.90, 2.33	0.130
Female	409 (64.21%)			
Severe neurological injury, n (%)				
Severe	354 (55.57%)	3.42	1.90, 6.13	0.000
Less severe	283 (44.43%)			
Number of pre-existing conditions	0 (n = 413, 64.84%)	ref.		
	1 (n = 155, 24.33%)	1.38	0.79, 2.39	0.256
	2 (n = 45, 7.06%)	1.76	0.78, 3.96	0.171
	≥3 (n = 24, 3.77%)	3.74	1.25, 9.57	0.006
Number of medical complications	0 (n = 353, 55.42%)	ref.		
	1 (n = 133, 20.88%)	1.02	0.53, 1.96	0.964
	2 (n = 74, 11.62%)	2.42	1.25, 4.69	0.008
	≥3 (n = 77, 12.09%)	2.69	1.43, 5.07	0.002

CI = confidence interval; n = number = OR odds ratio; SD = standard deviation.
Hosmer–Lemeshow goodness of fit: 0.95.

diabetes, peripheral vascular disease, cerebrovascular disease, rheumatic disease, chronic obstructive pulmonary disease, dementia, peptic ulcer disease, renal disease, any malignancy or metastatic solid tumor, hemiplegia or paraplegia, and liver disease. (see Appendix 1 under "pre-existing medical conditions" for the full list of ICD codes retained).

Identifying Medical Complications

To assess for in-hospital non-neurological medical complications, the MED-ECHO discharge abstract database was queried. All secondary diagnostic codes of the patients recorded during the index hospitalization for SAH were screened, and codes for acute illnesses that were previously identified in the SAH literature as non-neurological medical complications were retained.[2,9,13,22–24] The ICD codes were excluded from the list of retained medical complications if the diagnoses had been recorded in the 12 months prior to the index hospitalization to avoid misclassifying pre-existing conditions as medical complications. This method has been previously published.[18] The full list of in-hospital non-neurological medical complications retained included: malnutrition, respiratory failure, acute bronchitis, pneumonia, pneumothorax, pulmonary edema, hemothorax, gangrene, coagulation defect, anemia, acute renal failure, urinary tract infection, intestinal obstruction, gastrointestinal hemorrhage, acute liver disease, fluid and electrolyte imbalances, cardiac arrest (successful cardiac resuscitation), heart failure, acute myocardial infarction, and cardiac arrhythmias. (see Appendix 1 under "retained medical complications" for the full list of ICD codes and specific diagnoses).

Method to Establish Disease Severity (Neurological)

The severity of the neurological injury incurred by patients as well as the neurological complications was determined based on the ICD codes for coma, stupor, malaise, fatigue, vertigo, syncope, convulsion, collapse, somnolence, decreased level of consciousness, hydrocephalus, papilledema, cranial nerve abnormalities, paresis/plegia, and aphasia. The procedure codes included to determine the severity of neurological injury were those for ventriculostomy, intracranial pressure monitoring, cerebrospinal fluid diversion, and prolonged intubation. These diagnostic codes and procedure codes have been previously published as indicators of severe neurological injury in SAH[25] (see Appendix 1 under "severity of neurological injury retained codes" for the full list of ICD codes, and procedure codes retained). In our cohort, if a patient had any of these codes documented, they were grouped in the "severe neurological injury" group and if they had none of the codes queried, they were grouped in the "no severe neurological injury" group.

Statistical Analysis

All statistical analysis was conducted using STATA version 15 statistical software package StataCorp. 2017. Averages, standard deviations, frequencies, and proportions were calculated for age, sex, neurological status, pre-existing conditions, and medical complications (See Table 1). Analysis for the effect of age, sex, severe neurological injury, number of pre-existing conditions, and number of medical complications on the primary outcome was conducted via multivariate binary logistic regression analysis (See Table 1). The primary outcome was mortality at one year, which was determined by using patient death certificates. Age was analyzed as a continuous independent variable, while sex and the severity of neurological injury as categorical independent variables. The pre-existing conditions and medical complications were grouped in four groups, 0, 1, 2, and ≥ 3, and analyzed as categorical independent variables. Similarly, a multivariate binary logistic regression analysis with the binary outcome of

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Table 2: Multivariate logistic regression for ≥1 medical complications during hospitalization

Variable	OR	95% CI	*p* value
Age	1.01	1.00, 1.02	0.115
Sex (male)	1.19	0.84, 1.69	0.325
Severe neurological injury	3.54	2.52, 4.97	0.000
Number of pre-existing conditions			
0 (n = 413, 64.84%)	**ref.**		
1 (n = 155, 24.33%)	**1.51**	**1.02, 2.23**	**0.039**
2 (n = 45, 7.06%)	**2.03**	**1.06, 3.92**	**0.034**
≥3 (n = 24, 3.77%)	**3.78**	**1.47, 9.73**	**0.006**

CI = confidence interval; OR = odds ratio.
Hosmer–Lemeshow goodness of fit: 0.26.

having ≥1 in-hospital medical complication was performed, with the independent variables being age, sex, severe neurological injury, and the number of pre-existing conditions (categorical), as seen in Table 2. In Tables 3 and 4, the frequencies and proportions for specific pre-existing conditions and medical complications were calculated and their effects on the primary outcome (one-year mortality) were conducted via univariate binary logistic regression analysis. Finally, if variables were found to be associated with the primary outcome with a p value < 0.05 on the univariate logistic regression analysis in Tables 3 and 4, they were included in a multivariate logistic regression model, which also included, age, sex, and the severity of neurological injury as covariates (See Table 5).

Results

Descriptive Statistics: Demographics, Hospital Stay, and Discharge Status

The total number of patients in this cohort was 637. The youngest patient being 18 years old, and the oldest patient being 92 years old. The average length of stay of the hospitalization episode was 41.07 days (standard deviation 50.8 days), ranging from a minimum of 0 days to a maximum of 396 days. Fifty-one patients (8.0%) died at the institution where they were initially admitted, and 34 (5.3%) died over the course of the remainder of the hospitalization episode after transfer to another acute care facility. In terms of discharge status at the end of the hospitalization episode, 73.62% of patients were discharged home or home with services, 8.63% were discharged to a long-term care facility, 2.5% were transferred to another acute care hospital, 0.78% were discharged to a rehabilitation center, 0.47% left against medical advice, and 0.64% were discharged to another institution which was not specified.

Mortality: Effect of the Number of Pre-Existing Conditions and Medical Complications

Over the course of the whole hospitalization episode, 85 patients died, bringing the overall in-hospital mortality to 13.3%. At one year, a total of 94 patients had died, for an overall one-year mortality rate of 14.76%.

As seen in Table 1, the average age was 54.63 years (standard deviation 13.71 years). The majority of the patients were female (n = 409, 64.21%). Neither increasing age nor male sex was associated with increased mortality at one year. Severe neurological injury was associated with a 3.42-fold increase in mortality [95% CI 1.90–6.13]. Two hundred and twenty-four patients (35.16%) had at least one pre-existing conditions. While having 1 or 2 pre-existing conditions did not significantly increase mortality at 1 year, having 3 or more pre-existing conditions was associated with increased one-year mortality OR 3.74, [95% CI 1.25–9.57]. Two hundred and eighty-four patients (44.58%) had at least one medical complication over the course of their hospitalization episode. While having one medical complication was not associated with increased mortality, having 2 or ≥3 complications was associated with increased one-year mortality, OR 2.42 [95% CI 1.25–4.69] and OR 2.69 [95% CI 1.43–5.07], respectively. As seen in Table 2, in a multivariate logistic regression model controlling for age, sex, and the severity of neurological injury, having 1, 2, and ≥3 pre-existing conditions was associated with a 1.51-, 2.03-, and 3.78-fold increase in odds of patients having experienced at least 1 medical complication, respectively.

Mortality: Effect of Specific Pre-Existing Conditions and Medical Complications

As described in Table 3, malignancy (5.18%), hypertension (16.80%), diabetes (7.69%), and chronic pulmonary disease (6.44%) were found to be the most common pre-existing conditions and malignancy, diabetes, myocardial infarction, congestive heart failure, renal disease, and cerebrovascular disease were associated with increased one-year mortality on univariate logistic regression. As seen in Table 4, pneumonia (13.50%), fluid and electrolyte imbalances (12.87%), cardiac arrhythmias (7.38%), urinary tract infections (14.76%), and anemia (8.63%) were the most common medical complications recorded and sepsis, shock, respiratory failure, pneumonia, acute renal failure, fluid and electrolyte imbalance, acute myocardial infarction and cardiac arrhythmias were associated with increased one-year mortality on univariate logistic regression.

As demonstrated in Table 5, on multivariate logistic regression, controlling for age, sex, and the severity of the neurological injury, while none of the pre-existing conditions were found to be associated with increased mortality, sepsis, respiratory failure, and cardiac arrhythmias were found to be associated with increased mortality at one year.

Discussion

In this study, we have measured the effect of pre-existing conditions and medical complications on SAH mortality, while controlling for age, sex, and the severity of neurological injury. Of the 637 patients in our cohort, 94 died within a year of their initial SAH diagnosis (14.76%), of which 85 patients died during the hospitalization episode (13.3%). These mortality rates are similar to those previously reported for in-hospital and one-year mortalities (12.6%–13.9%), for SAH patients who were admitted to the hospital and underwent angiography or neurosurgical clipping of an aneurysm.[26,27] Male sex was not significantly

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Table 3: Frequency table for pre-existing conditions and univariate regression for mortality at one year, grouped by pre-existing condition

Pre-existing condition		Frequency	OR	95% CI	*p* value
Malignancy	Yes	33 (5.18%)	**2.29**	1.03, 5.09	**0.042**
	No	604 (94.82%)			
Dyslipidemia	Yes	30 (4.71%)	1.16	0.43, 3.12	0.763
	No	607 (95.29%)			
Hypertension	Yes	107 (16.80%)	1.53	0.89, 2.62	0.122
	No	530 (83.20%)			
Diabetes	Yes	49 (7.69%)	**2.26**	1.15, 4.44	**0.018**
	No	588 (92.31%)			
Peripheral vascular disease	Yes	10 (1.57%)	2.52	0.64, 9.64	0.185
	No	627 (98.43%)			
Myocardial infarction	Yes	9 (1.41%)	**4.78**	**1.26, 18.15**	**0.021**
	No	628 (98.59%)			
Congestive heart failure	Yes	10 (1.57%)	**3.98**	1.10, 14.37	**0.035**
	No	627 (98.43%)			
Renal disease	Yes	10 (1.57%)	**3.98**	1.10, 14.37	**0.035**
	No	627 (98.43%)			
Cerebrovascular disease	Yes	15 (2.35%)	**2.99**	1.00, 8.97	**0.050**
	No	622 (97.75%)			
Chronic pulmonary disease	Yes	41 (6.44%)	1.20	0.52, 2.80	0.666
	No	586 (93.56%)			
Hemiplegia or paraplegia	Yes	3 (0.47%)	2.91	0.26, 32.40	0.385
	No	634 (99.53%)			
Liver disease*	Yes	10 (1.57%)	–	–	–
	No	627 (98.43%)			
Rheumatic disease*	Yes	3 (0.47%)	–	–	–
	No	634 (99.53%)			
Peptic ulcer disease*	Yes	1 (0.16%)	–	–	–
	No	636 (99.84%)			
Dementia*	Yes	1 (0.16%)	–	–	–
	No	636 (99.84%)			

CI = confidence interval; OR = odds ratio.

*No deaths occurred in this group, so univariate logistic regression for one-year mortality not performed.

associated with mortality in our cohort OR, 1.45 [95% CI 0.90–2.33]. This finding is consistent with recent studies which show sex does not appear associated with mortality, when controlling for other risk factors including the severity of the neurological injury and age.[6–9,28]

In our cohort, age was not found to be associated with mortality OR, 1.00 [95% CI 0.99–1.02]. While several studies looking at new SAH patients have found that increasing age is associated with increased mortality,[6–10] a large institutional study looking exclusively at patients who were treated with angiography or neurosurgical clipping found that increasing age was not associated with increased mortality.[29] Our findings are consistent with this study and may be due to patients selected to undergo aneurysmal treatments are deemed medically and neurologically salvageable and may share similar clinical characteristics.

Compared to patients with no pre-existing conditions, having 1 or 2 pre-existing conditions did not significantly increase mortality at 1 year but having ≥3 pre-existing conditions was associated with increased one-year mortality OR 3.74, [95% CI 1.25–9.57]. Compared to patients with no medical complications, having 2 or ≥3 complications was associated with increased one-year mortality, OR 2.42 [95% CI 1.25–4.69], and OR 2.69 [95% CI 1.43–5.07], respectively, after controlling for age, sex, severity of neurological injury, and the number of pre-existing conditions.

When looking at which specific pre-existing conditions affect mortality, Norberg *et al.,* reported patients with a history of cardiac disease HR, 2.31 [95% CI 1.26–4.22], cerebrovascular disease HR, 2.35 [95% CI 1.19–4.66], and renal disease HR, 3.23 [95% CI 1.18–8.96], showed higher risks of mortality [36]. In our

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Table 4: Frequency table for medical complications and univariate regression for mortality at one year, grouped by medical complication

In-hospital complication		Frequency	OR	95% CI	*p* value
Sepsis	Yes	14(2.20%)	**8.33**	**2.82,24.60**	**0.000**
	No	623(97.80%)			
Shock	Yes	12(1.88%)	**4.30**	**1.34, 13.85**	**0.014**
	No	625(98.12%)			
Diabetes insipidus	Yes	3(0.47%)	2.91	0.26, 32.40	0.385
	No	634(99.53%)			
Skin ulcer	Yes	18(2.83%)	2.29	0.80, 6.58	0.124
	No	619(97.17%)			
Venous embolism	Yes	9(1.41%)	0.72	0.09, 5.82	0.757
	No	628(98.59%)			
Hypotension*	Yes	7(1.10%)	–	–	–
	No	630(98.90%)			
Malnutrition	Yes	21(3.30%)	1.38	0.45, 4.18	0.574
	No	616(96.70%)			
Respiratory failure	Yes	17(2.67%)	**7.08**	**2.66,18.86**	**0.000**
	No	620(97.33%)			
Acute bronchitis	Yes	2(0.31%)	5.83	0.36, 94.0	0.214
	No	635(99.69%)			
Pneumonia	Yes	86(13.50%)	**2.86**	**1.67, 4.86**	**0.000**
	No	551(86.50%)			
Pneumothorax	Yes	3(0.47%)	2.91	0.26, 32.40	0.385
	No	634(99.53%)			
Pulmonary edema	Yes	6(0.94%)	1.16	0.13, 10.02	0.895
	No	631(99.06%)			
Hemothorax*	Yes	1(0.16%)	–	–	–
	No	636(99.84%)			
Gangrene*	Yes	1(0.16%)	–	–	–
	No	636(99.84%)			
Coagulation defect	Yes	12(1.88%)	1.16	0.25, 5.37	0.851
	No	625(98.12%)			
Anemia	Yes	55(8.63%)	1.32	0.64, 2.72	0.455
	No	582(91.37%)			
Acute renal failure	Yes	19(2.98%)	**4.29**	**1.59,11.57**	**0.004**
	No	618(97.02%)			
Urinary tract infection	Yes	94(14.76%)	1.12	0.61, 2.03	0.722
	No	543(85.24%)			
Intestinal obstruction	Yes	4(0.63%)	1.94	0.20, 18.81	0.569
	No	633(99.37%)			
Gastrointestinal hemorrhage	Yes	7(1.10%)	2.34	0.45, 12.24	0.314
	No	630(98.90%)			
Liver disease	Yes	12(1.88%)	2.97	0.88, 10.08	0.080
	No	625(98.12%)			
Fluid and electrolyte imbalance	Yes	82(12.87%)	**1.77**	**0.99, 3.15**	**0.052**
	No	555(87.13%)			

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Table 4: *(Continued)*

In-hospital complication		Frequency	OR	95% CI	*p* value
Cardiac arrest*	Yes	1(0.16%)	–	–	–
	No	636(99.84%)			
Heart failure	Yes	14(2.20%)	2.37	0.73, 7.72	0.152
	No	623(97.80%)			
Acute myocardial infarction	Yes	20(3.14%)	**4.12**	**1.64,10.36**	**0.003**
	No	617(96.86%)			
Cardiac arrythmia	Yes	47(7.38%)	**4.20**	**2.22, 7.93**	**0.000**
	No	590(92.62%)			
Fever*	Yes	3(0.47%)	–	–	–
	No	634(99.53%)			

CI = confidence interval; OR = odds ratio.
*No deaths occurred in this group, so univariate logistic regression for one-year mortality not performed.

Table 5: Multivariate logistic regression for mortality at one year for specific pre-existing conditions and medical complications

Variable	OR	95% CI	*p* value
Age	1.00	0.99, 1.02	0.491
Sex (male)	1.26	0.76, 2.09	0.365
Severe neurological injury	**3.44**	**1.89, 6.25**	**0.000**
Malignancy	2.16	0.88, 5.30	0.092
Diabetes	1.69	0.78, 3.62	0.181
Myocardial Infarction	3.19	0.72, 14.15	0.126
Congestive heart failure	1.43	0.31, 6.51	0.644
Renal disease	3.43	0.72, 16.38	0.123
Cerebrovascular disease	3.00	0.87, 10.33	0.082
Sepsis	**4.95**	**1.37, 17.83**	**0.015**
Shock	1.12	0.27, 4.66	0.876
Respiratory failure	**4.13**	**1.33, 12.80**	**0.014**
Pneumonia	1.46	0.78, 2.72	0.241
Acute renal failure	1.17	0.33, 4.10	0.809
Fluid and electrolyte imbalance	1.28	0.67, 2.45	0.449
Acute myocardial infarction	2.41	0.79, 7.29	0.121
Cardiac Arrythmia	**2.86**	**1.39, 5.89**	**0.004**

CI = confidence interval; OR = odds ratio.
Hosmer–Lemeshow goodness of fit: 0.41.

cohort, we also reported cardiac disease, including congestive heart failure OR, 3.98 [95% CI 1.10–14.37], and myocardial infarction OR, 4.78 [95% CI 1.26–18.15], cerebrovascular disease OR, 2.99 [95% CI 1.00–8.97], and renal disease OR, 3.98 [95% CI 1.10–14.37, to be associated with increased mortality on univariate logistic regression analysis (Table 3). They had however also reported hypertension to be associated with increased mortality, HR, 1.74 [95% CI 1.18–2.57], which we did not, and they had not reported malignancy or diabetes to be associated, which we did OR, 2.29 [95% CI 1.03–5.09] and OR, 2.26 [95% CI 1.15–4.44], respectively. These differences may be due to several methodological differences including the use of chart review in the Norberg study to determine pre-existing conditions, a different geographic location (Montréal versus Sweden), and the fact we selected only patients who had undergone angiography or neurosurgical treatment of the aneurysm. Previous research on SAH has shown that geographic location can affect the risk of rupture of aneurysms. This is particularly true for Scandinavian countries which have been found to have a high risk of aneurysmal rupture when compared to North American countries.[30] Of note, on multivariate logistic regression, controlling for age, sex, the severity of neurological injury and medical

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complications (Table 5), none of the pre-existing conditions was found to be associated with increased mortality. As seen in Table 2, pre-existing conditions are associated with increased odds of patients having medical complications.

As seen in Table 5, we completed a multivariate logistic regression, controlling for age, sex, the severity of neurological injury, and the pre-existing conditions and medical complications that were found to be associated with increased mortality on univariate logistic regression ($p < 0.05$), in Tables 3 and 4. Looking at specific medical complications, respiratory failure was associated with increased mortality in our cohort OR, 4.13 [95% CI 1.33–12.80]. This finding is consistent with Solenski *et al.*, who reported that pulmonary complications were the most common cause of death in their cohort.[31] Sepsis was also associated with increased mortality OR, 4.95 [95% CI 1.37–17.83]. This is consistent with previous groups that had reported hypotension and fever to be associated with mortality.[9,15] Cardiac arrythmias were also associated with increased mortality OR, 2.86 [95% CI 1.39–5.89]. This is consistent with a large prospective study, which reported cardiac arrythmias to be associated with increased mortality, even when controlling for age, and the severity of neurological injury.[15] This is of particular interest because previous authors had reported that while common, cardiac arrythmias rarely lead to deaths.[31] Shock, pneumonia, acute renal failure, fluid and electrolyte imbalance, acute myocardial infarction were not found to be associated with increase mortality, on multivariate logistic regression analysis, which could be due to the relatively low power of the study. Fever, hypotension, hyperglycemia, and anemia were reported to be associated with increased mortality by previous authors.[9,15] In our cohort, these diagnoses were not associated with increased mortality. This could be due to the fact that these diagnoses are largely based on changes in vital signs and specific laboratory findings which may be more appropriate to collect in institutional cohorts, where these data can be obtained directly.

In our study, we found having 1, 2, and ≥3 pre-existing conditions was associated with a 1.51-, 2.03-, and 3.78-fold increase in odds of patients having experienced at least 1 medical complication, respectively (Table 2). This finding suggests that pre-existing conditions may increase mortality in SAH patients by increasing medical complications. While previous studies had described that pre-existing conditions were associated with increased mortality, the mechanism by which they do so is not well understood. Our study shows that it may be via an increase in medical complications. Further research should aim to better characterize the association between specific pre-existing conditions and specific medical complications.

This study has limitations. The identification of the diagnoses and of the procedures patients underwent was based on ICD-9, ICD-10, CPP, and CCI codes, with their associated risks of misclassification. This is a known limitation of administrative health data. That said, the codes for SAH have been validated by previous research and found to have very good accuracy.[2] We are therefore quite confident our patients were true aneurysmal SAH patients, especially considering we excluded patients with trauma codes and included only patients who had undergone angiography or neurosurgical clipping of an aneurysm. To avoid misclassification of pre-existing conditions, we have strictly used the same diagnostic codes previous authors had used when identifying pre-existing conditions using administrative health data.[32,33]

As with all administrative databases, there are limitations in the collection of clinical information. Specifically for our project, we used administrative health data to determine acute medical events and complications that occurred during the hospitalization of patients newly diagnosed with SAH. One of the risks of doing so is misclassifying concomitant ICD codes as acute when they are in fact pre-existing conditions. We took several steps to mitigate this risk. First, we excluded from the ICD codes for medical complications all the codes that had been previously documented as pre-existing conditions in our cohort. Second, we examined every diagnostic codes and only included those that were coding for diagnoses that had been classified as acute medical complications in the SAH literature.[9,15,31] Third, we have included in appendix 1 all the diagnostic codes that have been retained as medical complications. While there is a risk of misclassification, this methodology has permitted us to analyze the impact of important acute medical events on mortality.

Similarly, while the gold standard to assess the severity of the neurological injury is the use of the HH and WFNS scores, the variables used in our cohort to assess the extent of the neurological injury and neurological complications have been previously published.[25] Furthermore, the odds of mortality between the severe neurological injury group and the non-severe neurological group in our cohort OR, 3.42 [95% CI 1.90–6.13], mirror those published in institutional studies comparing HH 1–3 to HH 4 groups OR, 4.08 [95% CI 1.55–7.30].[10] One other limitation is the risk of misclassifying pre-existing conditions as medical complications. For medical complications occurring in hospital, to mitigate this risk, only codes that had not been given to patients the year prior to admission were retained and only a priori variables of interest based on the SAH literature were selected.[2,9,13,22–24] Another risk when assessing in hospital medical complications, interventions, and mortality for hospitalized patients using administrative health data is censoring due to patients transfers. To mitigate this risk, we constructed hospitalization episodes which included all transfers within 3 days of the initial SAH admission, as well as the subsequent transfer to another acute care hospital as part of the same hospitalization episode.

One limitation of the statistical analysis is that the models presented in Tables 1, 2 and 5 were not corrected for multiple testing. However, the variable selection described in the Methods section is commonly used, and correcting for multiple testing may be associated with an increased risk of false negatives.

Through the findings in this study, we have shown that pre-existing conditions have an important impact on SAH mortality. The effect measures provided can help physicians be better prepared when dealing with SAH patients with multiple comorbidities, especially those with malignancies, diabetes, congestive heart failure, renal disease, and cerebrovascular disease. By knowing the effect of these pre-existing conditions, on mortality and the increased risk of developing medical complications, physicians may opt for closer observation, monitoring, and laboratory testing for these patients. Importantly, these patients appear at risk of in-hospital medical complications, namely sepsis, respiratory failure, and cardiac arrythmias. Increased monitoring and aggressive management is warranted. Furthermore, public health measures to reduce pre-existing conditions should continue to be put forth. Last, this knowledge on the effect of medical complications on mortality can help physicians guide patients and families as they occur during the initial hospitalization.

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One of the major strengths of this study is the generalizability of our findings. The data collected by the PopHR database spanned 17 years, and multiple institutions. Furthermore, the known risk factors for SAH mortality were controlled for via binary multivariate logistic regression models, and the exposures included were collected over the course of the year preceding the initial hospitalization as well as the whole initial hospitalization episode. We opted to include in our analysis only patients who had undergone angiography or neurosurgical clipping of their aneurysm. We did so in order to establish an effect measure for pre-existing conditions and medical complications for patients that were deemed salvageable from a neurological standpoint at the time of admission. While this limits the generalizability of our findings to only patients undergoing procedures, it provides clinically relevant information for physicians caring for this patient population. Taken together, these findings can be generalized to patients newly diagnosed with SAH, admitted alive to an acute care hospital, and who undergo aneurysmal clipping or angiography, in a North American hospital, for patients covered by health insurance.

Conclusions

Pre-existing conditions and medical complications have been found to be associated with increased one-year mortality in SAH patients undergoing aneurysmal clipping or angiography. In particular, in-hospital complications are sepsis, respiratory failure, and cardiac arrythmias. Pre-existing conditions are associated with increased medical complications.

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Statement of Authorship

SS identified a gap in knowledge, completed the literature review, and proposed the research questions. DB and DP helped narrow the scope of the research questions, along with setting clear objectives. DB has been instrumental in providing access to the MED-ECHO database, the Régie de l'Assurance Maladie du Québec (RAMQ) billing codes database, and death certificate database. DB and DP have helped supervise and revised the writing of the thesis and manuscript. DB and DP have helped select the appropriate statistical tools for data analysis. SD has provided guidance regarding the clinical relevance of the thesis. The research methods were written by SS, with editorial assistance from DB and DP. The data analysis and interpretation were completed by SS.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.176

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