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Risk Factors of Severe Healthcare-Associated Adverse Events in a Tunisian Hospital: Results of a Case-Control Study

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Abstract: Adverse events (AE) are an ongoing challenge in healthcare. Apart from having a significant impact on patient morbidity and mortality, AE also result in increased healthcare costs due to longer hospital stays. However, little is known about AE occurrence and their risk factors in Tunisian healthcare system. To determine the incidence of severe adverse events (SAEs) and identify risk factors associated with SAE during hospitalization in a Tunisian University Hospital. A case-control study with incident cases was conducted including all patients hospitalized in the Teaching Hospital Farhat Hached within a one-month period in 13 clinical units. Medical records for caseswere selected by using stratified random sampling. The sample size was proportional to the number of admissions in each of 13 clinical departments. Controls were matched by the service and the duration of hospitalization preceding the appearance of SAE. Risk factors were collected and analyzed by conditional stepwise logistic regression. Overall, 304 controls were matched to cases, totalizing 456 patients. Multivariate conditional stepwise logistic regression analysis showed that night-time admission, hospitalization in the last six months, difficulty of communication, longer surgical operation, biopsy, presence of at least two medical devices, exposure to peripheral venous catheter, exposure to more than four medications and blood transfusion were considered as independent risk factors of SAE occurrence. Our results highlighted care-related risk factors such as catheters, blood transfusion and polymedication, which underlined the need to strengthen the care safety by focusing efforts especially in the field of hospital hygiene and infection control as well as pharmacovigilance.

Keywords: Adverse event Risk factor Patient Safety Health care quality.

INTRODUCTION

Recently attention has been focused worldwide on the issue of patient safety as a public health concernwith significant morbidity and mortality, andhigh economic burden on limited health resources [1]. One important indicator of patient safety is the rate of AEs among hospital patients. AEs are unintended injuries or complications that are caused by health care management, rather than by the patient's underlying disease, that lead to death, disability at the time of discharge or prolonged hospital stays [2, 3].

Previous retrospective record review studies in many countries have shown that 3% to 17% of hospitalised patients experience one or more AEs [4]. Some AEs are the unavoidable consequences of health care. However, half of AEs have been judged in retrospect to have been potentially preventable [1, 5]. Preventable AEs remain an ongoing challenge in healthcare [6].

In Tunisia, there are very few epidemiological data on the different forms that can take care-related AEs. Thus, a pilot study of AEs prevalence occurred in 2005 in the University Hospital of Monastir showed a prevalence around 10%, 60% of them were deemed preventable [7].

The purpose of this study therefore was to use a case–control study nested within a cohort study to identify risk factors independently associated with serious adverse events during hospitalization at University Hospital of Sousse F. Hached in order to guide prevention policy.

MATERIAL AND METHODS

Setting and sampling

The study was carried out in a Tunisian public university hospital, with 14 clinical departments (3 surgical and 11 medical departments). The total number of admissions was 37517 in 2015 with a mean length of stay about 4.15 days and an occupation rate of 80.5%.

A case-control study with incident cases was conducted. Controls were matched to cases according tooriginal service and length of stay before AEs occurrence. Data collection was carried out before SAE occurrence regardless the status "case" or "control", helping to better estimate care exposure.Cases and controls were identified from a prospective follow-up of patients hospitalized in our institutionfor 1 month.

Medical records for caseswere selected by using stratified random sampling. The sample size was proportional to the number of admissions in each of the 13 clinical departments. Admissions to psychiatric and neonatology departments, post partum less than 48 hours and day-only admissions were not included. OnlyAEs appeared or identified during hospitalization and during the observation period were included.

Definitions

An AE was defined as an injury caused by medical management, rather than the underlying disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. An AE was considered as severe if it prolonged the hospitalization, produced a disability at the time of discharge, or caused death [2].

A case was defined asa patient who, during his hospitalization and during the study period had presented a SAE.According to literature [2, 3, 5, 8, 9], only one SAE was retained when several SAE were clinically linked. However, if the events were not related, the final event or the most serious of those observed in the patient was considered. We then had a severe AE per patient.

Excluded were events occurred during hospitalization and identified before or after data collection, only SAE which occurred during the month of the surveywere included. Events that caused the hospitalization even if they occurred during the observation period and AEs whose serious nature was not confirmed in the medical report were excluded as well.

A control was defined asapatient randomly selected among patients who were hospitalized in the same service as the case, but who did not present any AE during his hospitalization.

Assuming a rate of SAE of 10% based on prior literature, a probability of a type 1 error of 5% with a power of 80% and OR required to lift difference between groups of 2.5, our study would require, when cases were matched with two controls, a sample of 390 patients with 130 cases and 260 controls.

The study was performed using a pre-tested questionnaire completed by physicians previously trained in the methodology of collection, according to a predefined timing. Six passages were made in each department during the study period. Some variables were collected at admission, in particular the general characteristics of the patient (age, gender ...), its clinical profile on admission (history of hospitalization in the last six months, immunosuppression,...) and admission characteristics (transfer, emergency admission,…).

Other variables were collected during each passage, referring to medical records and physicians, particularly exposure to invasive care procedures (surgery, biopsy...), to medical devices (venous catheter device, urinary catheter...) and health products (medicines, rehydration, blood and dietary products).

A couple of physician has reviewed all files of patients. For detection of a SAE we referred to a number of criteria, tested and validated in the literature [3, 8, 10, 11], and adapted to the objectives of our study. These criteria, nine in number were listed in Appendix A.

For each positive criteria, sufficient informations were writing in the questionnaire. If at least one criteria was positive, we considered that there was a suspected SAE. At the end of the data collection, all suspected SAEs and their consequences were reviewed and validated by an expert doctor outside the study (Professor of Medicine) in order to confirm or not the SAE.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 10.0

Quantitative variables were presentedas mean values with standard deviation. Qualitative variables were presented as absolute and relative frequencies with the corresponding 95% confidence intervals (95% CI).

In the univariate analysis, the Chi-square test or the Fisher's exact test was used to investigate the associations between the qualitative variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated.

Variables with a *p*-value less than 0.05 in the univariate analysis and those known in the literature as potential risk factors for SAEwere included in a binary logistic regression model for multivariate analysis, using the stepwise conditional method inorder to identify the independent risk factors for the occurrence of SAE by calculating the odds ratios (ORs) and the corresponding 95% CI.

- All tests were two-tailed, and a *p*-value of < 0.05 was considered significant.

- This study was approved by the IRB of our institution.

RESULTS

Patient, admission and healthcare exposure characteristics

During the study period, 1347 patients were observed in the 13 clinical departments included in the study, among them 152 patients had experienced at least one SAE confirmed by the medical expert. Based on the total of patients admitted during the study period, the incidence of at least one SAE per patient was 11.3% (95% CI [9.6 - 12.9]).

Figure-1 showed typology of SAE. Healthcare-associated infections were the most frequent SAE in our hospital with a proportion of 43.4%.

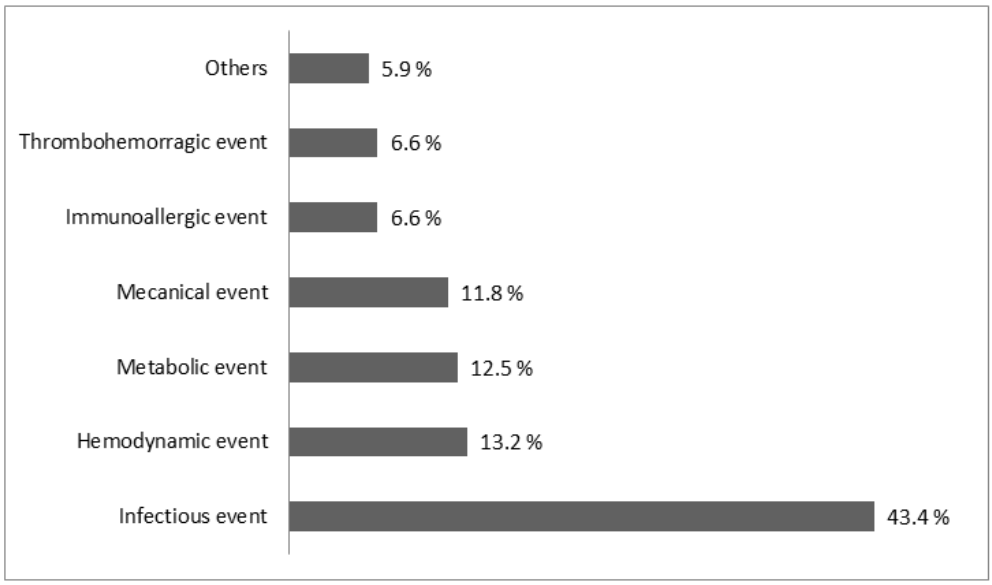

Fig-1: Typology of severe adverse events

Figure-2 showed SAE outcomes, most of SAE led to prolonged hospital stay (61%). Concerning the case-control study, 304 controls were matched to cases according to their services and hospitalization duration, thus a total of 456 patients were included in the study. The average age of the study population was 48.6 years ± 21.6 years and the sex ratio was 0.9.

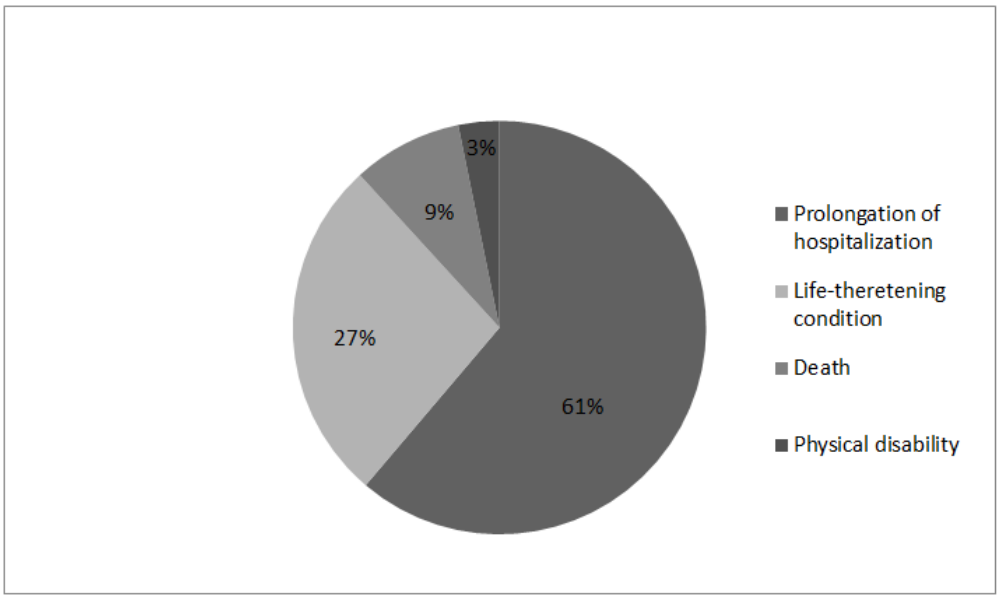

Fig-2: Severe adverse events outcomes

Only 29.2% had at least a history of hospitalization in the last six months and nearly half of them (49.8%) had at least one chronic disease. Emergency admission was the most frequent mode of admission (44.5%).

Nearly all patients (93.2%) received at least one medication during hospitalization, majority of them (76%) had been exposed to at least one invasive procedure and just over half of them (51.3%) had at least one medical device (Table-1).

Table-1: Patient, admission and healthcare exposure characteristics in Farhat Hached University Hospital (N=456)

VARIABLES	n (%)
PATIENTS CHARACTERISTICS	
Gender male	217 (47.5)
Smoking	134 (29.4)
Education level	
Illiterate and primary	248 (54.4)
Secondary and university	208 (45.6)
History of hospitalization in the last 6 months	133 (29.2)
Chronic disease	227 (49.8)
Immunosuppression	169 (37.1)
Charlson Comorbidity Index	
0 (Reference class)	162 (35.5)
1 – 2 (Medium comorbidity)	214
>= 3 (Severe comorbidity)	(47.0)
	80 (17.5)
Psychomotor agitation	36 (7.9)
Difficulty of communication	42 (9.2)
WHO Performance Status	
≥1 (partial or total dependence)	160 (35.1)
ADMISSION CHARACTERISTICS	
Transfer	63 (13.8)
Emergency admission	203 (44.5)
Night-time admission	175 (38.4)
Weekend admission	60 (13.2)
CARE EXPOSURE	
Exposure to at least an invasive procedure	347 (76.0)
Exposure to at least one medical device	234 (51.3)
Exposure to at least one health product	425 (93.2)

Factors associated with the occurrence of SAEs

Univariate analysis showed that history of hospitalization in the last six months, difficulty of communication, patient comorbidities, admission characteristics, exposure to specific care procedures, to medical devices and to healthy products was significantly more frequent in cases than controls (Table-2).

Multivariate conditional stepwise logistic regression analysis showed that night-time admission (OR= 1.7 [1.4 - 2.7]), hospitalization in the last six months (OR=1.8 [1.3 - 3.0]), difficulty of communication (OR = 2.2 [1.5 - 4.6]), longer surgical operation (OR = 5.6 [2.2 - 12.9]), biopsy (OR = 2.9 [1.3 - 6.9]), presence of at least two medical devices (OR = 3.1 [1.7 - 8.9]), exposure to peripheral venous catheter (OR=2.2 [1.1 - 4.4]), exposure to more than 4 medications (OR = 31.5 [3.9 - 250.1]), with both enteral and parenteral administration (OR= 1.3 [1.2 - 1.6]), and blood transfusion (OR= 3.4 [1.5 - 6.9]) were considered as independent risk factors of SAE occurrence (Table-2).

Table-2: Adverse events risk factors: Univariate and multivariate analysis

VARIABLES	Case n (%)	Control n (%)	Univariate analysis		Multivariate analysis (Final model)	
			Unadjusted OR [95% CI]	p	Adjusted OR [95% CI]	p
PATIENT CHARACTERISTICS						
Gender male	76 (50.0)	141 (46.4)	0.8 [0.5 – 1.3]	0.46		
Smoking	51 (33.6)	83 (27.3)	1.3 [0.8 – 2.0]	0.16		
History of hospitalization in the last 6 months	63 (41.4)	70 (23)	2.4 [1.5 – 3.6]	10^{-3}	1.8 [1.3 - 3.0]	0.02
Chronic disease	87 (57.2)	140 (46.1)	1.6 [1.1 – 2.3]	0.02	-	-
Immunosuppression	69 (45.4)	100 (32.9)	1.7 [1.1 – 2.5]	0.009	-	-
Charlson Comorbidity Index >= 3 (Severe comorbidity)	35 (47.9)	45 (26.6)	2.5 [1.4 – 4.5]	10^{-3}	-	-
Psychomotor agitation	19 (12.5)	17 (5.6)	2.4 [1.2 – 4.7]	0.01	-	-
Difficulty of communication	22 (14.5)	20 (6.6)	2.4 [1.2 – 4.5]	0.007	2.2 [1.5 - 4.6]	0.03
WHO Performance Status *≥1 (partial or total dependence)*	63 (41.4)	97 (31.9)	1.5 [1.1 - 2.2]	0.045	-	-
ADMISSION CHARACTERISTICS						
Transfer	29 (19.1)	34 (11.2)	1.9 [1.1- 3.2]	0.023	-	-
Emergency admission	78 (51.3)	125 (41.1)	1.5 [1.1- 2.2]	0.039	-	-
Nighttime admission	72 (47.4)	103 (33.9)	1.7 [1.2 - 2.6]	0.005	1.7 [1.4 - 2.7]	0.03
Weekend admission	27 (17.8)	33 (10.9)	1.8 [1.1 - 3.1]	0.04	-	-
CARE EXPOSURE						
Exposure to invasive procedures						
Surgical intervention	43 (28.3)	71 (23.4)	1.29 [0.8 - 2.0]	0.25	-	-
Duration of intervention>75thp	25 (16.4)	15 (4.9)	3.8 [1.9 - 7.4]	10^{-3}	5.6 [2.3 - 12.9]	10^{-3}
General anesthesia	37 (24.3)	50 (16.4)	1.7 [1.03 - 2.73]	0.036	-	-
Biopsy	24 (15.8)	18 (5.9)	2.9 [1.5 - 5.7]	10^{-3}	2.9 [1.3 - 6.9]	0.008
Puncture	24 (15.8)	34 (11.2)	1.5 [0.8 - 2.6]	0.16	-	-
Endoscopy	20 (13.2)	29 (9.5)	1.4 [0.7 - 2.6]	0.24	-	-

Conventional radiology with injection of contrast agents	30 (19.7)	42 (13.8)	1.5 [0.9 - 2.5]	0.1	-	-
<u>Exposure to medical devices</u>						
Number of medical devices						
0	11 (7.2)	75 (24.7)	1	-	1	-
1	81 (53.3)	153 (50.3)	3.6 [1.8 -7.2]	10^{-3}	1.9 [0.7 – 4.9]	0.18
≥2	60 (39.5)	76 (25.0)	5.4 [2.6 -11.0]	10^{-3}	3.1 [1.7 – 8.9]	0.03
Medical devices type						
Urinary catheter	50 (32.9)	67 (22.0)	1.7 [1.1 – 2.6]	0.01	-	-
Peripheral venous catheter	140 (92.1)	226 (74.3)	4 [2.1 - 7.6]	10^{-3}	2.2 [1.1 – 4.4]	0.03
Gastric probe	35 (23.0)	42 (13.8)	1.9 [1.1 – 3.0]	0.013	-	-
Mechanical ventilation	42 (27.6)	53 (17.4)	1.8 [1.1 – 2.8]	0.011	-	-
<u>Exposure to health products</u>						
Number of medication						
0	1 (0.7)	30 (9.9)	1	-	1	-
1- 4	49 (32.2)	191 (62.8)	7.7 [1.1 -57.8]	0.04	7.8 [0.9 – 62.0]	0.05
>4	102 (67.1)	83 (27.3)	36.9 [4.9-276.0]	10^{-3}	31.5 [3.9 – 250.1]	0.001
Drug administration route						
Enteral	23 (92)	93 (74.8)	1	-	1	-
Parenteral	35 (94.6)	100 (76.3)	1.3 [0.7 – 2.4]	0.31	1.07 [0.3 – 1.5]	0.37
Enteral + parenteral	93 (97.9)	81 (72.3)	4.4 [2.5 – 7.5]	10^{-3}	1.3 [1.2 – 1.6]	10^{-3}
Blood product	28 (18.4)	19 (6.3)	3.4 [1.8 - 6.3]	10^{-3}	3.4 [1.5 – 6.9]	0.003
Rehydration product	96 (63.2)	114 (37.5)	2.8 [1.9 - 4.3]	10^{-3}	-	-
Dietary product	18 (11.8)	14 (4.6)	2.8 [1.3 - 5.7]	0.006	-	-

DISCUSSION

The major strength of this study was the estimation of the risk of SAEs occurrence using a global approach including all types ofSAEs based on data collected prospectively [12]. Data collection was carried out before SAE occurrence regardless the status "case" or "control", helping to better estimate care exposure.

However, we have adopted nine criteria for the selection of the AEs inspired from the 18 criteria previously validated in the Australian study of AEs [3]. However; validation to our Tunisian context is still required.

Our study showed that an estimated 11.3% of patients admitted to our institutionexperienced one or more SAEs during the index admission. This incidence is quite similar to the incidence reported inthe university hospital of Monastir (Tunisia) which was 11.7% [7] but it exceeds incidence of SAE found in patients hospitalized in the internal medicine division at the Mongi Slim University Hospital in Tunis which was 5.2% [13], although, many methodologicaldifferences can be noted with variations in inclusion criteria for eligible events.It exceeds also the median incidence reported in the literature which was 9.2% [11]. However, the incidence in Australia and New Zealand was significantly higher. In fact, current variation in methodology and definitions, as well as setting and year, make it difficult to assess whether there are intrinsic differences in AE occurrence between healthcare systems [14].

According to intrinsic risk factors, our studyrevealed no statistically significant difference in the average age and distribution by gender between cases and controls. However, many previous studies have shown that SAEincidence increases significantly with age.

Thus, a recent meta analysis showed that adverse outcomes occurred in one-third of discharged older patients [15]. Moreover, among patients aged 65 and older, the risk of SAE was 2.5 times higher when other intrinsic risk factors such as chronic diseases or other comorbid conditionswere presents [16, 17]. The existence of twoor more chronic diseases in the same patient would be a predisposing factor to develop a SAE.

In this context, a dose-response effect was found such that the subject with an intrinsic risk factor had an AE in 10.5 of all cases, which rose to 15.1% when there were 2 risk factors involved and to 22.9% when there were 3 or more risk factors ($p<0.001$) (16).

In our study, the presence of at least one chronic disease was 1.6 time higher among cases in univariate analysis but this association did not remain significant after adjustment for history of hospitalization in the last six months. Thus, Hastings showed that hospitalization within the previous 6 months (HR= 1.70 [1.30-2.22]) was independently associated with higher risk of SAE [18]. Our study reinforces this outcome. A valid prospective approach, the Charlson comorbidity index [19, 20] has been applied to classify comorbid conditions of patients. Nevertheless, higher Charlson comorbidity index, both in our study as the one conducted in Quebec [21] had not shown in multivariate analysis, significant increased risk of SAE occurrence. Furthermore, a highly significant and stable association has been demonstrated through several studies between patient communication problems and risk of occurrence of SAE during hospitalization [21–23]. Bartlett found that patients with communication problems such as aphasia or dysarthria were three times more likely to experience preventable AE [21]. Besides, in a large North American survey, Iezzonifound that participants with major disability affecting communication were more likely to be dissatisfied with physicians' understanding of their conditions, with the time spent discussing their problems and answering questions and so more prone to medication dangers and other risks associated with inadequate communication, as well as communication problems during medical procedures [22]. Our study has confirmed these findings.

Among admission characteristics, only night-time admission seems to be an independent risk factor for AE occurrence. However, as has been reported in some studies, weekend admissions experience significantly higher rates of adverse health outcomes [24, 25]. The 'weekend effect' has been attributed to reduced hospital staffing and/or access to specific intensive treatments and procedures performed on the weekend [26, 27].

Healthcare-associated infections were found to be the major type of SAEs, especially in surgery. A longer operative time has been shown to increase the surgical site infection risk [28–30].This increase occurs when the operative time is above the 75th percentile. In a study of 56,216 primary total knee arthroplasties, Namba *et al*., found a 9% increase in the surgical site infection risk for each 15-minute increase in operative time [31]. Besides, Kable *et al.*, found in an Australian study that the risk of SAEs was 5.5 times higher when operating time was over 180 minutes compared with a duration of less than 60 minutes (OR=5.5; 95% IC [3.3 - 9.2]) [28]. When interpreting these findings, the possibility that a longer operative time may reflect intra-operative complications or greater procedural complexity should be taken into account [32].

Other invasive procedures have been explored, in particular biopsy, puncture, endoscopy and conventional radiology with injection of contrast agents. Among these procedures, only biopsy seems to be associated with an increased SAE risk.

However, it has been well established that the biopsy related risks are likely affected by the competence of the operator and the team (nursing, anesthesia, and technicians), the details of the specific procedure being performed, and the patient's anatomy, demographics, and health status.This result should be the subject of further investigations in order to identify factors that may predict biopsy related AEs and so, prospective risk assessment might enhance the quality of informed consent and facilitate decisions regarding procedural appropriateness [33]. Concerning exposure to health products, polymedicationproved to be an independent factor of multiple adverse events.Thus, our study showed that taking more than four drugs during hospitalization multiply the risk of SAEs by 31. Our findings were in line with those from previous research which revealed that the number of drugs prescribed seemed to be one of the most important independent predictor for receiving an inappropriate medication [34–36]. In addition, polymedication is often associated with unexpected side effects, not observed during monotherapy [37, 38].

The systemic review performed by de Vries et alshowed that 11-24% of SAEs observed in Canada, Australia, the USA, Great Britain and New Zealand were related to medication which represents the second cause of SAEs after operation related events. Almost half ofthese drug-related events could be avoided, especially in the elderly, through an adequate reporting system [11].

Medical devices represent another independent risk factor for occurrence of SAEsin our study. The frequency of simultaneous or sequential exposure to two or more medical devices is 3 times higher among cases. It is twice higher if the medical device was a peripheral venous catheter. Furthermore, other medical devices had shown no association with the risk of SAE. Similar findings were reported in the literature.In Spain, the odds of suffering a hospital-related adverse event was 1.6 times for patients with invasive devices, such as peripheral venous catheter or urinary drainage system [17]. An Australian study had also shown that the risk of SAEs would increase with exposure to invasive procedures in surgical patients [39].

These results prompt to implement effective reporting and learning systems on adverse events in healthcare in order to establish the extent of error and adverse events; monitor trends; develop effective interventions; observe changes following the introduction of those interventions and share learning on which interventions are effective or are not, especially in the areas of medication and medical device safety with the pharmacovigilance and medical device vigilance systems, which are already in operation in many health systems in developed countries. Periodic analysis of the effectiveness and appropriateness of these various systems should take place [16]. Ultimately, these mechanisms aim to establish a transparent, open and honest patient safety culture in healthcare.

In conclusion, our study is an exhaustive analysis of intrinsic and extrinsic risk factors that may cause SAE in a Tunisian university hospital.

Indeed, our results highlighted care-related risk factors such as catheters, blood transfusion andpolymedication, which must raise the joint professional awareness and get under way of programs and policies which strengthen the care safety by focusing efforts especially in the field of hospital hygiene and infection control as well as pharmacovigilance in order to ensure patient safety within the healthcare system. These actions are crucialfor the development of a culture of continuing professional developmentand the creation of indicators measuring the quality of care. Although the risk related to intrinsic risk factorsis unavoidable, it is nevertheless important to promote a policy of risk management in Tunisian hospitals in order to control extrinsic risk factors for SAE occurrence.

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Appendix A

- Unwanted physical or mental impairment occurred during the index admission
- Unplanned ablation, injury or repair of an organ or tissue during or subsequent to an invasive procedure or during a vaginal delivery
- Passage or unplanned return to the operating room during the index admission
- Unplanned conversion from laparoscopic to open surgery
- Any life-threatening accident in short-term
- Dissatisfaction with care documented in the medical record
- Unplanned transfer to an intensive care unit or intensive care unit
- Unplanned transfer to another institution of health
- Unexpected death

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