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Clinical paper

Polypharmacy prior to in-hospital cardiac arrest among patients with cardiopulmonary diseases: A pilot study

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Abstract

Background: Patterns of medication administration prior to in-hospital cardiac arrest (I-HCA) and the potential impact of these on patient outcomes is not well-established. Accordingly, types of medications administered in the 72 h prior to I-HCA were examined in relation to initial rhythms of I-HCA and survival.

Methods: A retrospective, pilot study was conducted among 96 patients who experienced I-HCA. Clinical characteristics and treatments including medications were extracted from electronic health records. Relative risk (RR) of medications or class of medications associated with the initial rhythms of I-HCA and return of spontaneous circulation (ROSC) were calculated.

Results: Two distinct sub-groups were identified that did not survive to hospital discharge (n = 31): 1) those who received either vasopressin/desmopressin (n = 16) and 2) those who received combinations of psychotherapeutic agents with anxiolytics, sedatives, and hypnotics (n = 15) prior to I-HCA. The risk of pulseless electrical activity and asystolic arrest was high in patients who received sympathomimetic agents alone or in combination with β-Adrenergic blocking agents, (RR = 1.40, 1.41, respectively). Vasopressin and a combination of vasopressin and fentanyl were associated with risk of unsuccessful ROSC (RR = 2.50, 2.38, respectively).

Conclusions: The types of medications administered during inpatient care may serve as a surrogate marker for identifying patients at risk of specific initial rhythms of I-HCA and survival.

Keywords: In-hospital cardiac arrest, Survival, Polypharmacy, Initial Rhythms of Cardiac Arrest

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Introduction

In-hospital cardiac arrest (I-HCA) is a significant public health problem, with approximately 200,000 cases treated in the United States each year.[1] I-HCA is associated with high morbidity and mortality, and only 20−25% of patients survive to hospital discharge.[1,2] Studies assessing the impact of pharmacological treatments on the onset and outcome of I-HCA are very limited. A few recent reports have described an association between patient deterioration (e.g., I-HCA) and the administration of sedatives and analgesics, particularly opioids, either alone or in combination with additional sedatives.[3−5] Although a variety of medications are often used in the management of acutely ill hospitalized patients, the patterns of medication administered prior to I-HCA and their role in survival is unknown.

There is no standardized definition of polypharmacy and it encompasses quantitative (e.g., number of medications) or qualitative (e.g., combinations of specific medications) aspects of medication use.[6,7] Polypharmacy has been associated with adverse effects specifically due to age-related physiological processes including compromised renal and hepatic drug excretion that ultimately influence pharmacokinetic and pharmacodynamic effects.[7] Polypharmacy is recognized as an increasingly serious problem that costs the United States health care system more than $177 billion annually.[8]

Mortality due to cardiovascular disease events is increasing globally and is associated with normal aging.[9] Medications that prevent cardiovascular diseases and their complications are frequently used among older populations and may cause decreased heart rate and changes in heart rhythms.[10] Moreover, managing complex conditions by medications that influence the autonomic nervous and cardiovascular systems can be very challenging for patients in acute and intensive care units (ICU). The purpose of this study was to identify clusters and types of medications administered in the 72 h prior to I-HCA and the associated relative risk of initial rhythms of I-HCA and survival. We chose to study medications that influence the autonomic nervous and cardiovascular systems due to their effects on cardiac electrophysiology. The preliminary data reported here will serve as the foundation for developing predictive models to identify hospitalized patients at high-risk for untoward cardiac outcome.

Methods

Study design and setting

This retrospective, observational study was conducted by using a database containing information about hospitalized patients who experienced I-HCA (2014−2016) from a large urban academic hospital. The study was approved by the Institutional Review Board associated with the health system.

Sample

Records of patients who experienced I-HCA and underwent cardiopulmonary resuscitation (CPR) equal or greater than 1 min during the observation period were extracted from the institution's Electronic Health Record (EHR) and screened for study eligibility. Patients were eligible if they were ≥18 years of age, experienced I-HCA in an acute care (step-down) or in an ICU; received at least two medications within 72 h prior to I-HCA (polypharmacy); and had a history of structural cardiopulmonary disease. Patients must have experienced at least one of the following conditions: documented a history of structural heart diseases including coronary artery disease, myocardial infarction (MI), percutaneous coronary intervention or coronary artery bypass graft surgery (CABG), cardiomyopathy, and valvular diseases. Signs and symptoms of heart failure were confirmed by physician documentation during the hospitalization in which the I-HCA occurred, and by echocardiogram showing left ventricular systolic dysfunction (EF < 50%). Pulmonary disease diagnoses (e.g., chronic obstructive pulmonary disease, pulmonary hypertension) were confirmed if listed in the medical history. Patients with a history of cardiopulmonary diseases who experienced stroke or complications after CABG (e.g., sternal bleeding after cardiac surgery) were also included in the study. The rational for selecting patients with a history of cardiopulmonary diseases was based on evidence that most patients who experienced I-HCA often had a history of cardiac and pulmonary diseases.[11,12] Only the first episode of I-HCA was recorded during the period of hospitalization.

Patients were excluded if the I-HCA was due to trauma, recreational drug overdose, hypothermia, chronic terminal illness such as cancer (stage IV and/or active treatments including radiation therapy and chemotherapy), human immunodeficiency virus infection (HIV), or bleeding other than intracranial or cardiovascular hemorrhage (e.g., gastrointestinal bleeding); and I-HCA during procedures (e.g., intubation). The effect of cancer and HIV on developing cardiovascular diseases is not fully understood and the underlying mechanism(s) for developing disease may differ from the traditional pathway(s) of developing or progressing heart diseases.[13,14]

Patients who were comatose (not related to administered sedatives) or received resuscitation therapy as the result of error where "Do Not Resuscitate" documentation could be found in the medical charts were also excluded. In addition, I-HCA documentation about resuscitation treatments (i.e., digital code blue sheets in EHR) that did not have complete demographic data (i.e., time, date, initial rhythms) were not utilized for the study.

We identified medication(s) 72 h prior to I-HCA because I-HCA may occur variably during hospitalization of each patient. Furthermore, it encompasses both short and long acting medications. The mean ± standard deviation of age of hospitalized patients experienced I-HCA has been reported 66.5 ± 15.8.[15] As physiological status declines among aging population, the metabolism of medications is altered due to comorbidities (e.g., decreased kidney function).

Measures

Clinical characteristics of the eligible patients were obtained by extracting the data from EHR by trained research assistants. The Kappa statistic for interrater reliability of the abstracted data between the research assistants and the PI was >90%. Left ventricular ejection fraction (EF) measured by the echocardiograms and the 12 lead-electrocardiograms (ECG) were obtained only if were available during hospitalization periods in which I-HCA occurred; if multiple EF measurements and 12- lead ECGs were present, the ones most proximal to the event were selected. The 12-lead ECGs were studied in relation to QTc intervals using Fridericia formula. ECGs were excluded for the presence of paced signals, left bundle branch block

(LBBB), flattened T- wave, artifacts, and rhythms other than sinus rhythm. These conditions (e.g., LBBB) obscure the accuracy of QTc measurements by conventional methods. A cardiac electrophysiologist reviewed the ECG data blindly and confirmed the results. Laboratory data including potassium (K^+), magnesium (Mg^{++}), an estimate glomerular filtration rate (eGFR) and creatinine clearance (Cockcroft-Gault), were obtained within 72 h prior to cardiac arrest. Causes of mortality were extracted from the standardized mortality form signed by a physician.

Procedures were defined as those considered therapeutic interventions (e.g., angiograms) but excluded those restricted to invasive line insertion (e.g., central or arterial lines). Time to I-HCA was calculated in days from the date of surgery/procedure for patients who had surgery (e.g., coronary artery bypass graft) or a procedure. If multiple surgeries/procedures occurred prior to I-HCA on different days, time to I-HCA was calculated as the number of days from the mean or median of the surgeries'/procedures' days to I-HCA. Dates, times, and underlying causes of mechanical intubation prior to I-HCA were collected. The Acute Physiology and Chronic Health Evaluation II (APACHE II) is a severity-of-disease classification system which has been used to predict different outcomes in a variety of populations.[16] In this study, APACHE II scores 24 h prior to I-HCA were calculated by collecting the worst values in each category of physiological measurements.

The Primary independent variable, medications administered within 72 h of I-HCA were extracted from the EHR. Only those medications that were signed off as administered by clinicians (nursing staff) were collected. Generic medications were classified according to the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification system (PTC). The second-and third-tier hierarchies were selected for each medication because they were the least broad for categorizing groups of medications with the least amount of skewed data. To identify the unique combinations of medications by generic name and AHFS classification, we used the Apriori algorithm for frequent itemset mining (FIM).[17] In FIM, the goal is to identify item sets (clusters) of items that occur with a frequency above a specified threshold (e.g., present in over 2% of the dataset for these analyses) by making multiple passes through the data. The first step is to simply count the occurrence of each medication. The next step then counts pairs of frequently occurring medications using the specified threshold of 2% of the data. If the pairs did not meet the threshold, they were "pruned." This process was repeated increasing the number of medications examined in each itemset, until no more itemsets were generated. We only counted a medication or a class of medication once though some patients received more than one medication with the same classification.

The primary dependent variables were initial rhythms of I-HCA and survival. The initial rhythms were classified as the presence of pulseless electrical activity (PEA) and asystole or ventricular tachycardias and ventricular fibrillation (VT/VF). Survival was referred to as return of spontaneous circulation (ROSC) which occurred as a result of resuscitation treatments and survival to hospital discharge. We selected ROSC for our major statistical analyses because complex conditions are usually present in post-arrest (e.g., shock).[18] Additionally, different therapeutic treatments (e.g., hypothermia) are involved[19,20] as confounding variables which may not reflect physiological/pathophysiological changes prior to cardiac arrest. Electronic code sheets from EHR were used to collect data about the initial rhythms and ROSC.

Statistical analysis

Descriptive statistics of continuous variables are reported using means and standard deviations (SD) or, medians and interquartile ranges while categorical variables are reported using frequencies and percentages. The Chi-square and Fisher's Exact tests, odds ratio and 95% confidence intervals were calculated to investigate the relationship between medications, classes of medications, and the dependent (outcome) variables: initial rhythms of I-HCA and ROSC (survival). Relative risk (RR) was calculated for medication(s) and class of medications in relation to outcome variables. This was a pilot study with a small sample size and did not test any hypotheses with the main goal to obtain estimates of effect sizes for powering larger studies. Results with a p-value <0.05 for relative risk (RR) were considered statistically significant and reported. Data construction and statistical analyses were performed using Python version 2.7.2, SPSS version 24 (SPSS, Inc.; Chicago, Illinois) and SAS version 9.4 (SAS Institute, Inc.; Cary, NC) software.

Results

A total of 698 patients during the observation period were screened from the hospital's designated database that contained a list of patients who experienced I-HCA. One hundred (100) patients met the inclusion and exclusion criteria; of these, four (4) patients were excluded because they did not meet our definition of polypharmacy; having two or more medications administered prior to I-HCA. Thus, a total of 96 patients' records were abstracted.

The study patients' clinical characteristics are presented in Table 1. The mean $\pm$ standard deviation of the APACHE II score was 28 ± 8 within 24 h prior to I-HCA. The mean $\pm$ standard deviation of administered medications by patients was 11 ± 5 medications within 72 h of I-HCA. Other clinical characteristics, including admission diagnoses are presented in Appendix.

In total, 85 patients (89%) had 12-lead ECG prior to I-HCA, but only 38 (45%) had 12 lead ECGs that measured QTc intervals. The following ECGs were excluded (47, 55%): 14 (16%) due to atrial fibrillation or atrial flutter, 13 (15%) due to paced signals, 6 (7%) due to LBBB, 2 (2%) due to combination of atrial fibrillation with either paced signals or LBBB, and 12 (14%) due to the presence of artifacts or flattened T waves. The mean $\pm$ SD of the prolonged QTc ($\geq$480 ms) were present in 10 (26%) patients; 530 ± 0.03 ms. The time interval between the recorded 12-lead ECG and I-HCA was: median, one day or 24 h, IQR 0.1-3.7 days.

Medications and survival

All patients who received vasopressin/desmopressin (n = 16) or a combination of psychotics, anxiolytics, sedatives, hypnotics (PASH agents, n = 15) did not survive to hospital discharge. The clinical characteristics of these two groups of patients are summarized in Table 2 with type of PASH medication in Table 3. Fentanyl was co-administered to all patients who received vasopressin/desmopressin. In this group of patients, norepinephrine was administered to 13 (87%) patients, 58 ± 37 h prior to I-HCA, and vasopressin was administered (n = 15) patients, 40 ± 34 h prior to I-HCA.

The medications most frequently combined with PASH agents were fentanyl, aspirin, furosemide, and albuterol. Patients with history of depression (n = 8) received anti-depressants along with

Table 1 – Clinical Characteristics of Study Patients (n = 96).

Variables	
Age	69 ± 15
Female, Sex	29 (30%)
Location of cardiac arrest (ICU)	52 (54%)
Initial Rhythm of Cardiac Arrest (VT/VF)	29 (30%)
Survival	
Return of Spontaneous Circulation (ROSC)	60 (63%)
Hospital Discharge	21 (22%)
Length of Stay (LOS)	
LOS-Admission to Unsuccessful ROSC and Death after ROSC	7 days (IQR, 15)
LOS-Admission to Hospital Discharge	24 days (IQR, 41)
Ejection Fraction	45 ± 21
Body Mass Index (BMI)	30 ± 8
Cardiovascular Risk Factors	
Hypertension	92 (96%)
Hyperlipidemia	51 (53%)
Diabetes Mellitus	53 (55%)
History of Cardiac Diseases (n = 91)	
Coronary Artery Diseases	76 (79%)
Myocardial Infarction	38 (40%)
Cogestive Heart Failure	57 (59%)
Coronary Artery Bypass Graft	18 (19%)
Cardiomyopathy	31 (32%)
Implanted Heart Devices (Pacemaker, ICD)	20 (21%)
Left Ventricular Assist Device	1 (1%)
Dialysis	18 (19%)
Sepsis on Admission or during Hospitalization	25 (26%)
Pulmonary Diseases (e.g., COPD)	26 (27%)
Sugery/Procedure (n = 51)	
Cardiac	44 (86%)
Non-Cardiac	7 (16%)
Causes of Intubation (n = 36)	
Respiratory or Airway Protection	15 (42%)
Hemodynamic Instabilities	9 (25%)
Surgery/Procedure	10 (28%)
Others	2 (6%)
Causes of Mortality (n = 75)	
Cardiac Diseases	38 (51%)
Pulmonary Diseases	14 (19%)
Others (e.g., sepsis, renal failure)	21 (28%)
No documentation	2 (3%)

VT/VF, Ventricular Tachycardia/Ventricular Fibrillation; ICU, Intensive Care Unit; ROSC, Return of Spontaneous Circulation.

medications which were used for sedation (e.g., midazolam), delirium (e.g., aripiprazole), anxiety (e.g., alprazolam), and sleep (e.g., melatonin). The remaining patients (n = 7) who did not have documentation of a history of depression by physicians received PASH agents for sedation (e.g., dexmedetomidine HCL), delirium (e.g., alprazolam), anxiety (e.g., citalopram), and sleep (e.g., trazodone).

The EF and APACHE II scores of patients who received PASH agents trended lower compared to patients who received vasopressin/desmopressin (Table 2). The pertinent lab values specifically major electrolytes, kidney functions, and renal clearance are presented in Table 4 which demonstrates renal impairment by the eGFR and CrCl among all patients.

Relative risk of initial rhythms of I-HCA and ROSC associated with medication(s) administered prior to I-HCA

The RRs associated with the PEA/asystolic arrest and unsuccessful ROSC based on classification of medication(s) administered are presented in Table 5. Sympathomimetic agents alone or in combination with β-Adrenergic blocking agents were associated with higher risk of PEA/asystolic arrest, (RR = 1.40 and 1.41, respectively) compared to VT/VF arrests. Moreover, patients who received Sympathomimetic agents and β-adrenergic blocking agents along with either anti-thrombotic or diuretics medications did not incur any additional risk of PEA/asystolic arrest (RR = 1.3). The same finding of no additive risk of PEA/asystolic arrest was observed for the combination of β-Adrenergic blocking agents with loop diuretics (RR = 1.3) and a combination of β-adrenergic blocking agents, loop diuretics, and anticoagulants (RR = 1.3). Patients who received platelet-aggregation inhibitors had a 69% lower risk of PEA/asystolic arrest and a 2.7 folds higher risk of VT/VF arrest compared to patients who did not receive these medications. Additionally, patients who received a combination of platelet-aggregation inhibitors and opiate agonists had a 73% lower risk of PEA/asystolic arrest and almost a two-fold increase in risk of VT/VF arrest compared to patients who did not receive this medication combination. Patients who received a combination of fentanyl and vasopressin or vasopressin/

Table 2 – Characteristics of Patients Who Received Vasopressin/Desmopressin or PASH Agents and Did Not Survive to Hospital Discharge.

Clinical Characteristics	[a]Vasopressin, Desmopressin (n = 16)	Combination of Psychotics, Anxiolytics, Sedatives, Hypnotics (n = 15)
Age	66 ± 13	68 ± 21
Sex, Female	2(13%)	3(20%)
Ejection Fraction	48 ± 20	35 ± 18[b]
Intitial Rhythms		
VTVF	5 (31%)	4 (27%)
PEA/Asystole	11 (69%)	11 (73%)
Location of cardiac arrest		
ICU	16 (100%)	7 (47%)
Return of Spontaneous Circulation (ROSC)		
Successful	4 (25%)	10 (67%)
Unsuccessful	12 (75%)	5 (33%)
Intubation, 72 h Prior to I-HCA		6 (40%)
Sepsis	9 (56%)	4 (27%)
Dialysis	3 (19%)	2 (13%)
APACHE II 24 h prior to I-HCA (n = 16, n = 7)	32 ± 11	25 ± 10
12-Lead ECG		
QTc interval (ms, n = 8, n = 1)	470 ± 0.04	420 ± 0.0
Surgeries/Procedures		
Cardiac	7 (44%)	6 (40%)
Non-cardiac	3 (19%)	3 (19%)

[a] Antidiuretics is the classification for vassopressin and desmorpressin.
[b] Ejection fraction, marginally significant compared to the rest of patients who did not receive PASH agents(p = 0.08).

desmopressin had higher risk of unsuccessful ROSC that those who did not received these medications.

Discussion

In this retrospective study, patients who received vasopressin/desmopressin or PASH agents did not survive to hospital discharge; this group composed 32% of the total patients. Our findings demonstrated a statistically significant risk of immediate mortality (lack of ROSC) for patients who received vasopressin/desmopressin. The clinical risk of mortality for patients who received either vasopressin/desmopressin or PASH agents was demonstrated by the lack of survival to hospital discharge. Those who received vasopressin/desmopressin had higher APACHE II scores prior to I-HCA compared to the rest of patients at ICUs which may suggest higher mortality risk and they might not have a chance to survive either with or without vasopressin/desmopressin. Moreover, our study provides an insight into potential mechanism(s) of developing certain initial rhythms by examining clinical characteristics including polypharmacy and laboratory values. Administering a combination of sympathomimetic (adrenergic) agents and β-Adrenergic blocking agents (Appendix) is a common clinical practice. However, their roles in the genesis of PEA/asystolic arrest has not been previously studied and warrants further investigation. The clinical characteristics (e.g., laboratory values) may also have played an important role in I-HCA occurrence considering that the renal dysfunction is evident from eGFR and crCl of all patients. Furthermore, approximately half of the available ECGs could not be studied due to pathological conditions (e.g., LBBB, heart rhythm devices) and we did not have the records of initial rhythms of I-HCA. Therefore, we could not examine the relationship between prolonged QTc and polymorphic VT. Future studies will include a record of initial rhythms of I-HCA to investigate the proportion of polymorphic VT and its association with a variety of non-antiarrhythmic medications (e.g., antibiotics).[21]

Vasopressin, an antidiuretic hormone, is often administered in combination with other potent medications (e.g., fentanyl), yet the magnitudes of their interactions and their effects are still unknown. Animal and human studies of the effects of opioids on arginine vasopressin have been inconclusive.[22] Fentanyl has been shown to increase arginine vasopressin release in healthy volunteers and

Table 3 – Types of PASH Medications Administered to Patients Who Did Not Survive to Hospital Discharge (n = 15).

Psychotherapeutic Agents	Number of Single Administered Medication to Patients
Haloperidol	5
Quetiapine	4
Paroxetine	1
Aripiprazole	2
Venlafaxine	1
Bupropion	1
Trazodone	2
Sertraline	3
Citalopram	1
Escitalopram	1
Mirtazapine	1
Anxiolytics, Sedatives, Hypnotics	
Midazolam	3
Lorazepam	3
Dexmedetomidine HCL	5
Alprazolam	2
Zolpidem	1
Melatonin	7
Ramelteon	1

Table 4 – Laboratory **V**alues 72 Hours Prior to I-HCA**.**

All Subjects (n = 96)	0–23 Hours	24–47 Hours	48–72 h
Potassium (mmol/L)	4.5 ± 0.8	4.3 ± 0.6	4.4 ± 0.6
Magnesium (mEq/L)	1.9 ± 0.4	1.8 ± 0.3	1.9 ± 0.3
Estimated Glomerular Filtration Rate (mL/min/1.73^2)	45 ± 29	45 ± 28	45 ± 28
Creatinine Clearance (mL/min)	43 ± 37	42 ± 32	42 ± 33
Patients Who Received Antidiuretics (n = 16)			
Potassium (mmol/L)	4.6 ± 0.6	4.3 ± 0.7	4.5 ± 0.6
Magnesium (mEq/L)	2.0 ± 0.2	1.9 ± 0.3	2.0 ± 0.4
Estimated Glomerular Filtration Rate (mL/min/1.73^2)	60 ± 11	56 ± 10	56 ± 11
Creatinine Clearance (mL/min)	40 ± 24	38 ± 23	42 ± 26
Patients Who Received PASH Agents (n = 15)			
Potassium (mmol/L)	4.5 ± 0.5	4.4 ± 0.4	4.6 ± 0.6
Magnesium (mEq/L)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2
Estimated Glomerular Filtration Rate (mL/min/1.73^2)	54 ± 39	55 ± 40	55 ± 37
Creatinine Clearance (mL/min)	56 ± 52	60 ± 55	60 ± 53

Table 5 – The Most Considered Medications and Class of Medications Associated with Increased Risk of PEA/Asystolic Arrest and Survival**.**

Initial Rhythms of I-HCA				Relative Risk (RR) of PEA/Asystolic arrest	
Medications	**Total Nubmer of Initial Rhythms (VT/VF and PEA/Asystolic Arrests)**	**Number of PEA/Asystolic Arrests (n = 67)**	**Number of VT/VF Arrests (n = 29)**	**RR (95% CI)**	***P***
Sympathomimetic (Adrenergic) Agents	60	47	13	1.40 (1.02–1.94)	0.04
Sympathomimetic (Adrenergic) Agents, β-Adrenergic Blocking Agents	35	30	5	1.41 (1.11–1.80)	0.01
Sympathomimetic (Adrenergic) Agents, β-Adrenergic Blocking Agents, Antithrombotic	31	26	5	1.33 (1.04–1.69)	0.02
Sympathomimetic (Adrenergic) Agents, β-Adrenergic Blocking Agents, Diuretics	27	23	4	1.34 (1.05–1.69)	0.02
Loop Diuretics, β-Adrenergic Blocking Agents	35	29	6	1.33 (1.04–1.70)	0.02
Anticoagulants, loop diuretics, β-Adrenergic Blocking Agents	27	23	4	1.34 (1.05–1.69)	0.02
Platelet-aggregation inhibitors	52	30	22	0.69 (0.53–0.90)	0.01
Platelet-aggregation Inhibitors, Opiate Agonists	37	21	16	0.73 (0.53–0.99)	0.05
Return of Spontaneous Circulation (ROSC)				**Relative Risk (RR) of Unsuccessful Resuscitation**	
Medications	**Total number of Resuscitations**	**Successful ROSC (n = 60)**	**Un-successful ROSC (n = 36)**	**RR (95% CI)**	***P***
Antidiuretics (Vasopressin/desmopressin)	16	4	12	2.50 (1.61–3.88)	<0.001

surgical patients.[22] Moreover, the side effects (e.g., myocardial ischemia, hyponatremia) of vasopressin have been assessed only in small studies and have been associated with higher lactate.[23] A combined systematic review and meta-analysis of 26 studies of I-HCA and out-of-hospital cardiac arrests which included both children and adults revealed no evidence of neurological improvement with administration of adrenaline or vasopressin. Only six studies focused strictly on I-HCA, five of which were published 15 or more years ago; the findings of these studies therefore may not be generalized to all patients who currently suffer cardiac arrest.[24] Furthermore, none of the I-HCA studies investigated the relationship between vasopressors prior to cardiac arrest and their potential roles in ROSC. The lack of survival of patients who received vasopressin/desmopressin in this study, despite the small sample size, demands further research into the role of vasopressors in populations with different underlying pathological conditions and experiences I-HCA.

A combination of PASH agents is currently being used in hospitalized patients to treat a wide variety of overlapping conditions, including insomnia, anxiety, delirium, behavioral disturbances, and pain.[25,26] Some of these conditions (e.g., delirium) have been associated with poor patient outcomes and increased risk of mortality.[27] Moreover, depression is more prevalent in cardiovascular patients than in the general population.[28] Our finding is congruent with previous studies demonstrating that PASH agents were used for a variety of clinical conditions including cardiovascular disease (e.g., heart failure)[29] and delirium. Approximately more than half of patients who received PASH agents had documented history of depression. One normal dose of antidepressant in patients with severe heart disease can lead to adverse events including heart block, ventricular arrhythmias, and loss of myocardial contraction.[28] Clinicians still lack clear guidelines for using antidepressants among patients with cardiovascular diseases.[28]

There are contradictory results about the use of PASH agents in relation to adverse events (e.g., mortality) both in the general population and hospitalized patients.[30–38] Despite the complexity of available medications, large-scale placebo controlled clinical trials are needed to provide robust evidence demonstrating the effects of these medications and their interactions on patient outcomes in acutely and critically ill patients.[27,39]

Strengths and limitations

This descriptive study had a small sample size and was conducted within a single institution. We selected patients with similar medical histories to ensure a homogenous sample rather than mixing all types of comorbidities and underlying pathological disorders, the I-HCA population is heterogenous.[40] Additionally, only patients who had documentation of >1 min CPR were included which have might excluded patients who were more likely to survive. This might lead to selecting a small sample size and to an unequal proportion of patients with PEA/asystolic arrest versus VT/VF arrest. Therefore, the results should be viewed with caution before drawing population-based conclusions. However, the proportion of PEA/asystolic arrests has been reported to be larger than VT/VF arrests even in studies with large sample sizes.[11,41,42] Future studies with a larger sample size and a control group can be planned to validate our findings. These studies will include the dosages and half-life of medications, and will examine whether administered medications are included as a part of patients' history. The literature continues to lack evidence for the therapeutic roles of some medications, as well as their interactions; our study increases the awareness of such data for future research.

Conclusions

Anticipation of specific initial rhythms of I-HCA by examining clinical characteristics may assist clinician in preparing and/or providing more focused monitoring and thereby may ultimately increase survival to hospital discharge. On the other hand, anticipation of low survival depending on individual's clinical characteristics (e.g., medications, severity of illness) may assist clinicians in preparing patients' families about end of life issues prior to the time of cardiac arrest.

Declaration of competing interest

The authors declare that they have no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2020.100026.

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