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IN HOSPITAL OUTCOME OF VENTRICULAR ARRHYTHMIA STORM AT THE AGA KHAN UNIVERSITY HOSPITAL, KARACHI, PAKISTAN

Ibrahim Gul[1], Aamir Hameed Khan[2], Musa Karim[3], Ayemen Shakeel Mirza[4]

1 KRL Hospital Islamabad, Pakistan
2 The Aga Khan University
3 National Institute of Cardiovascular Diseases Karachi, Pakistan
4 Louisiana State University Shreveport, USA

Address for Correspondence:
Dr. Ibrahim Gul
Consultant Cardiologist, KRL Hospital Islamabad, Pakistan
Email: dr_gul96@yahoo.com

Contribution
IG conceived the idea and designed the study. Data collection and manuscript writing was done by IG, AHK, MK, and ASM. All the authors contributed equally to the submitted manuscript.

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ABSTRACT

Objective: Our objective was to know the percent mortality of ventricular arrhythmia (VA) storm, its major leading factor and the predictors of in-hospital mortality of VA storm in our population.

Methodology: In this retrospective observational study conducted at The Aga Khan University Hospital Karachi, all patients with age ≥16, with VA storm were included. Baseline demographic, clinical characteristics, laboratory parameters and management interventions were recorded in pre prepared questionnaire. The data was analyzed using SPSS version 21.

Results: Of the total 74 patients, 86.5% were male, 77% were having monomorphic VT and 60.8% were in pulmonary edema. Hypertension (73%), IHD (63.5%), DM (48.6%) MR (56.8%) TR (50%) and LV dysfunctions were the commonest risk factors of VA storm. The mean hospital stay was 5.64 ± 5.63 and 59.5% patients were discharged home in stable condition. On bivariate analysis female gender, polymorphic VT, pulmonary edema, intubation, baseline hemoglobin levels, and baseline WBC counts were predictors of in-hospital mortality of VA storm with hazard ratios (HR) of 2.22 [0.95-5.18], 2.44 [1.18-5.08], 13.49 [1.82-99.85], 17.54 [2.38-129.44], 1.25 [1.05-1.47], and 1.06 [1.01-1.11] respectively. On multivariate analysis, female gender, intubation, and baseline hemoglobin level were independent predictors of in-hospital mortality of VA storm with adjusted HRs of 3.88 [1.02-14.77], 9.9 [0.95-103.25], and 1.47 [1.2-1.79] respectively.

Conclusion: VA storm mortality for conservative management in our region is comparable to the international figures. Also we have similar risk factors for VA storm like low EF, structural heart disease and similar predictors of in-hospital mortality for VA storm.

Keywords: Ventricular arrhythmia storm, Electrical storm, Monomorphic ventricular tachycardia, Polymorphic ventricular tachycardia, Implantable Cardioverter defibrillator, Radiofrequency ablation, Electrofulgration, Ganglionectomy

INTRODUCTION

Ventricular arrhythmia (VA) storm or electrical storm (ES) has been recognized as a separate arrhythmia syndrome characterized by the occurrence of three or more than three VA episodes during 24 hours interval.[1] The exact mechanism of ES is unknown but it has been proposed, through animal models and studies on human beings, that it is caused by focal myocardial denervation followed by excessive innervation, resulting in enhanced regional or global sympathetic activity, which eventually translates into ventricular arrhythmias.[2, 3] ES is associated with high morbidity and mortality even in the presence of Implantable Cardioverter Defibrillator (ICD).[4] Exner et al. conducted a study on patients with ICD implanted for secondary prevention and found that there was 5.6 fold increased death during the first 12 weeks and 2.4 fold increased death during first 3 years in those who suffered ES as compared to those who did not have ES although they had other ventricular arrhythmias.[5] It has been argued through various studies that each defibrillator shock multiplies into mortality.[6] More over the psychological effects of the shocks on the patient is another serious problem.

Treatment options available for ventricular arrhythmia storm are very limited. Currently, the recommended management is considered to be radiofrequency ablation with trans-coronary ethanol ablation as a last resort in case radiofrequency ablation fails.[7] Other options are surgical ablation, electrofulgration, cervical sympathetic ganglionectomy, thoracic epidural anesthesia and renal denervation.[3, 8, 9] Medical management includes anti-arrhythmic drugs like amiodarone, b-blockers etc, which are much inferior to the ablation therapy but are used where ablation facilities are not available.[10]

The problem is further fortified by the fact that our understanding of the condition is very limited. Very scarce data is available on its pathogenesis, treatment and outcome especially in the developing countries like Pakistan. Hence the aim of the current study was to find out the percentage mortality, to determine the factors associated with and to identify the predictors of cardiac and all-cause mortality in patients with ventricular arrhythmia storm in our region.

METHODOLOGY

This was a retrospective observational study in which data of patients admitted to Aga Khan University Hospital from January 2009 to September 2014, with the diagnosis of VA storm/ES was collected from patient profile and computerized record using a structured questionnaire and then was analyzed for the various parameters related to ventricular arrhythmia storm.

All patients with the age of 16 and above who presented with VA storm whether treated medically or with some intervention, whether they had prior ICD implanted or not and whether they were ventilated or not, were included in this study. Those arrhythmia patients not fulfilling the criteria for ES were excluded from the study

ES storm was defined as (i) recurrent VA in a short time (≥3 separate episodes in 24 h, each requiring termination by intervention), (ii) frequent defibrillator therapies (≥3 separate episodes separated by 5 min in 24 h), or (iii) incessant VA (continuous VA that recurred promptly despite intervention for termination over 12 h)

All-cause mortality was defined as death in the selected patient's population due to any cause whether cardiac or non-cardiac whereas cardiac mortality was defined as death related directly to the VA storm. An arrhythmia was classified as Ventricular Tachycardia (VT) if it fulfilled the following criteria: (1) Wide QRS morphology with a polarity changed from that in sinus rhythm. (2) There is regular RR interval. (3) There is ventriculo-atrial dissociation. (4) Sudden onset of tachycardia.

An arrhythmia fulfilling the above criteria but with irregular RR interval, at a heart rate of less than 250 bpm was classified as polymorphic VT. If the RR interval was irregular and the heart rate was more than 250 bpm, it was classified as Ventricular fibrillation (VF).

VT in the setting of ICD device was defined as an episode with a ventricular rate of more than 150 bpm. Similarly VF in the setting of ICD device was

defined as an episode with a ventricular rate of more than 188 bpm.

Hemodynamic instability was defined as systolic blood pressure less than 90mm Hg or the patient was on inotropic support. Comorbidities were both self-reported or diagnosed during hospital stay. Diabetes mellitus (DM) was defined as according to American diabetes association.[11] Hypertension was defined as blood pressure (BP) more than 140/90 mmHg as measured with the help of a mercury sphygmomanometer of an appropriate sized cuff or the patients was already on antihypertensive medicine. Chronic kidney disease (KCD) was defined as Glomerular filtration rate (GFR) less than 60 ml/min/1.73m^2 for three or more months. Ischemic heart disease (IHD) was defined either on the basis of coronary angiography (CA) as stenosis more than 50% in any of the epicardial coronary arteries as visually assessed, or myocardial perfusion imaging (MPI) or stress echocardiography (SECH) positive for ischemia.

Ischemic cardiomyopathy was defined as left ventricular dysfunction, assessed through echocardiography, due to coronary artery disease diagnosed either on the basis of CA or MPI or SECH. Non ischemic cardiomyopathy was defined as left ventricular dysfunction in the setting of a normal CA or MPI or .SECH. Ejection fraction (EF) was calculated echocardiographically by visual estimation method.

Selected demographic and historical data like age, gender, type of arrhythmia, hemodynamic status, underlying comorbidities, any device previously implanted, any treatment given and outcome of the patients, were collected from the available record, according to the prepared questionnaire. Diagnosis of ES or any other arrhythmia was made by Electro physiologist after thoroughly assessing the clinical details, ECGs, rhythm strips and or the programmer data entered in the file. The device already implanted is analyzed routinely in Aga Khan University Hospital by the specified programmer according to the protocol of our department.

Descriptive statistics were presented as mean ± SD for continuous variables, and numbers with frequencies for categorical variables. The outcome of interest was defined as cardiac and all-cause death determined through standardized procedures described in the methods section. Observations were censored if subjects are discharged following recovery, or are lost to follow up due to any other reason. In the bivariate analyses, cox proportional hazards regression were used to identify variables eligible for entry into multivariable analysis (p-value >0.10). After removing some variables on account of multi-collinearity, a purposive multivariate cox proportional hazards regression model was build taking hospital length of stay (days) as time variable and in-hospital mortality as status variable. The estimates were presented as hazard ratios (HR) along with 95% confidence intervals (CI). Kaplan Mayer curves were presented for significant variables. A p-value of ≤ 0.05 was considered significant. All the analysis were performed using IBM SPSS version 21.

RESULTS

A total of 74 patients were included in this study. Out of them, 86.5% (64) were male. Majority 77% (55), had monomorphic VT at presentation and 60.8% (45) were presented in pulmonary edema. Detailed baseline characteristics are presented in Table 1.

Table 1: Baseline Characteristics of patients

Characteristics	Total
Total (N)	74
Gender	
Male	86.5% (64)
Female	13.5% (10)
Ventricular arrhythmia at the time of presentation	
Monomorphic Ventricular tachycardia	57 (77%)
Polymorphic Ventricular tachycardia	16 (21.6%)
Ventricular fibrillation	11 (14.9%)
Unspecified Ventricular Arrhythmia	1 (1.4%)
Hemodynamic status at the time of presentation	
Hemodynamically unstable	26 (35.1%)
Pulmonary edema	45 (60.8%)
Intubate	42 (56.8%)
Associated Factors and Cardiac History	
Diabetes mellitus	36 (48.6%)
Hypertension	54 (73%)
Ischemic heart disease	47 (63.5%)
Chronic kidney disease	16 (21.6%)
Ischemic cardiomyopathy	3 (4.1%)

Non-ischemic cardiomyopathies	12 (16.2%)
Prior CABG	8 (10.8%)
Prior PCI	15 (20.3%)
Ejection Fraction (Median [IQR]) %	20 [25-15]
Cardiac Structural and Devise History	
Diastolic dysfunction	12 (16.2%)
Mitral regurgitation (MR)	42 (56.8%)
Aortic regurgitation (AR)	17 (23%)
Mitral stenosis (MS)	2 (2.7%)
Aortic stenosis AS	2 (2.7%)
Tricuspid regurgitation (TR)	37 (50%)
Device Implanted	23 (31.1%)
ICD dual chamber	4 (5.4%)
ICD Single chamber	19 (25.7%)

ICD = implantable cardioverter-defibrillator, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention, IQR = interquartile range

Most of the patients presented to us with monomorphic VT (77%) and in pulmonary edema (60.8%). More than half were intubated (56%). Amongst the various risk factors, majority were having hypertension (73%), IHD (63.5%) and DM (48.6%). All patients presented to us were having severe left ventricular dysfunction with estimated average EF of 20%. MR (56.8%) and TR (50%) were the two most common structural abnormalities in our patients. We had only 31.1% patients with device already implanted.

We used multiple drugs but the most commonly used were amiodarone (89.2%), sedatives (81.1%), B-blockers (75.7%) antibiotics (64.9%) and lidocaine (60.8%). Almost all of the patients received some form of intervention with the most common intervention used was direct current (DC) shock (75.7%). The mean hospital stay of our patients was 5.64 ± 5.63. We discharged home 59.5% of patients in stable condition. The main management tools and outcome of our patients are given in Table 2.

Table 2: Management and Outcomes

Characteristics	Total
Total (N)	74
Medical Treatment	
Amiodarone	66 (89.2%)
Sotalol	5 (6.8%)
Lidocaine	45 (60.8%)
B-blockers	56 (75.7%)
Sedatives	60 (81.1%)
General anesthetic	32 (43.2%)
Antibiotics	48 (64.9%)
Interventional treatment	70 (94.6%)
Overdrive pacing	6 (8.6%)
Direct current (DC) shock	53 (75.7%)
Radiofrequency ablation	5 (7.1%)
Surgical ablation	3 (4.3%)
Other	3 (4.3%)
Outcomes	
Length of hospital stay (days)	
Range	1 to 28
Mean ± SD	5.64 ± 5.63
Median [IQR]	4 [7.25 - 2]
Discharge Status	
Alive	44 (59.5%)
Expired	30 (40.5%)

SD = standard deviation, IQR = interquartile range

On bivariate analysis female gender, polymorphic VT, pulmonary edema, need of intubation, baseline hemoglobin levels, and baseline white blood cells counts were found to be associated with increased in-hospital mortality with hazard ratios (HR) of 2.22 [0.95-5.18], 2.44 [1.18-5.08], 13.49 [1.82-99.85], 17.54 [2.38-129.44], 1.25 [1.05-1.47], and 1.06 [1.01-1.11] respectively.

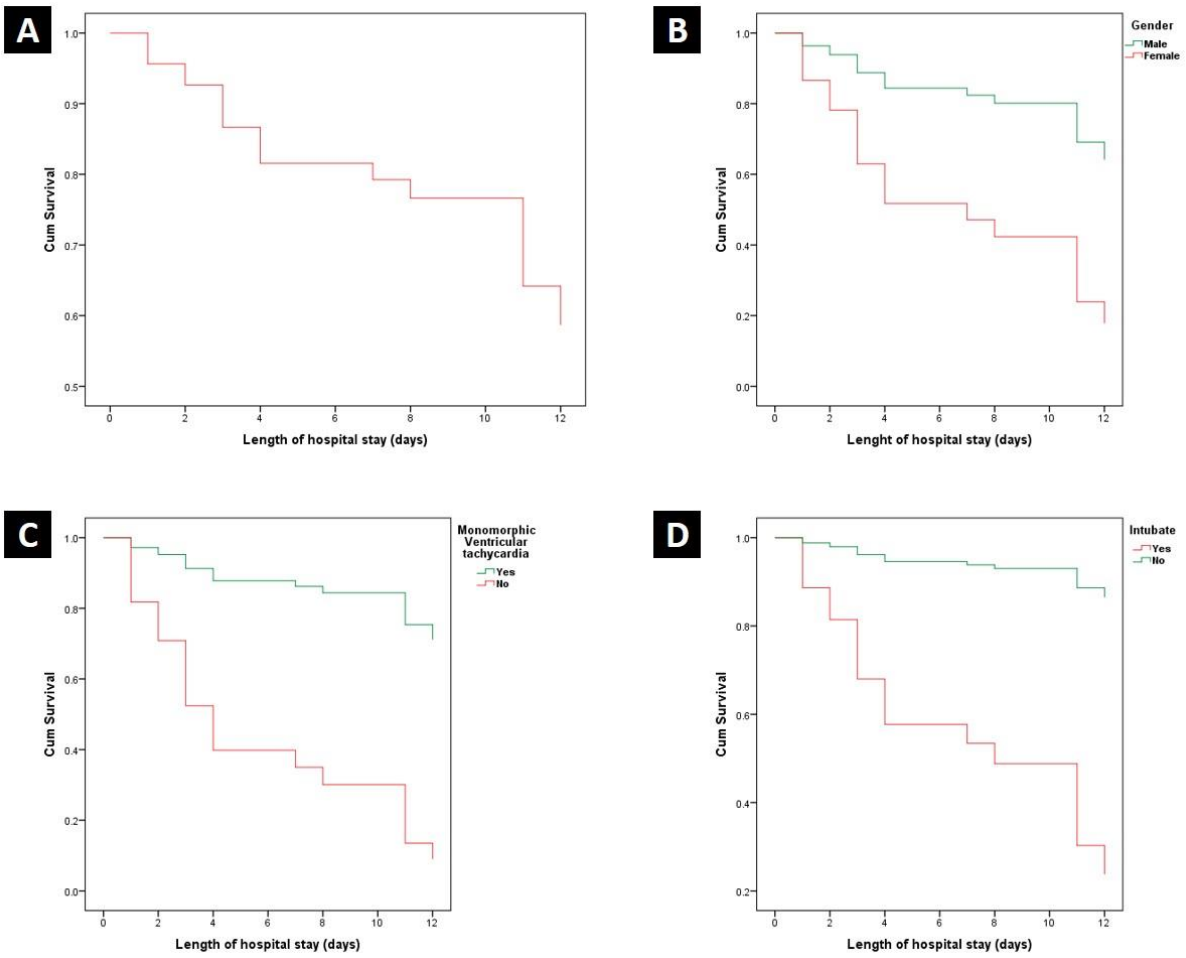
On multivariate analysis the female gender, need for intubation, and baseline hemoglobin level were independent predictors of in-hospital mortality with adjusted HRs of 3.88 [1.02-14.77], 9.9 [0.95-103.25], and 1.47 [1.2-1.79] respectively. Mortality rate (%) by various characteristics, bivariate and multivariate Cox-Regression analysis for in-hospital mortality and Kaplan Mayer survival curves for the significant variables are presented in Table III and Figure 1.

Table 3: Mortality rate (%) by various characteristics and bivariate and multivariate Cox- Regression analysis for in-hospital mortality of patients with electrical storm

Characteristics	NO	Mortality rate %(n)	Bivariate		Multivariate	
			HR[95%CI]	P-value	HR[95%CI]	P-value
Female	10	70%(7)	2.22 [0.95-5.18]	0.006	3.88 [1.02-14.77]	0.047*
Ventricular arrhythmias at the time of presentation						
Monomorphic VT	57	31.6% (18)	0.42 [0.2-0.87]	0.02*	0.14 [0.03-0.69]	0.016*
Polymorphic VT	16	75% (12)	2.44 [1.18-5.08]	0.017*	0.22 [0.04-1.19]	0.078
VF	11	54.5% (6)	1.23 [0.5-3.02]	0.645	_	_
Hemodynamic status at the time of presentation						
Hemodynamically unstable	26	3.8% (1)	0.09 [0.01-0.68]	0.02*	0.35 [0.02-5.2]	0.448
Pulmonary edema	45	64.4% (29)	13.49 [1.82-99.85]	0.011*	_	_
Intubated	42	69% (29)	17.54 [2.38-129.44]	0.005*	9.9 [0.95-103.25]	0.055
Risk factors and cardiac history						
DM	36	55.6% (20)	2.12 [0.99-4.54]	0.054	1.19 [0.48-2.96]	0.715
Hypertension	54	40.7% (22)	0.79 [0.35-1.79]	0.57	_	
IHD	47	44.7% (21)	1.67 [0.76-3.66]	0.2	_	
CKD	16	43.8% (7)	0.67 [0.28-1.62]	0.375	_	
ICMP	3	66.7% (2)	3.69 [0.83-16.51]	0.087	1.96 [0.36-10.57]	0.435
NICMP	12	33.3% (4)	0.65 [0.23-1.88]	0.432	_	
Prior CABG	8	37.5% (3)	0.78 [0.24-2.58]	0.684	_	
Prior PCI	15	60% (9)	2.02 [0.91-4.46]	0.082	1.13 [0.45-2.83]	0.787
Cardiac structural and device history						
Diastolic dysfunction	12	50% (6)	1.44 [0.59-3.53]	0.426	_	_
Mitral Regurgitation (MR)	42	33.3% (14)	0.59 [0.29-1.22]	0.153	_	_
Aortic Regurgitation(AR	17	23.5% (4)	0.42 [0.15-1.	0.106	_	_
Mitral stenosis (MS)	2	100% (2)	_	_	_	_
Aortic stenosis (AS)	2	100% (2)	_	_	_	_
Tricuspid Regurgitation (TR)	37	24.3% (9)	0.35 [0.16-0.76]	0.008*	0.55 [0.21-1.44]	0.225
Device implanted	23	17.4% (4)	0.38 [0.13-1.1]	0.075	_	_
Baseline Investigations						
Ejection Fraction (%)	_	_	1 [0.97-1.05]	0.81	_	_
Hemoglobin (g/dL)	_	_	1.25 [1.05-1.47]	0.01*	1.47 [1.2-1.79]	<0.001*
White blood cells (1000/uL)	_	_	1.06 [1.01-1.11]	0.022*	1.01 [0.95-1.06]	0.809
Platelets (thousand/uL)	_	_	1 [0.998-1.003]	0.973	_	_
Sodium (meq/L)	_	_	0.98 [0.93-1.04]	0.517	_	_
Potassium (meq/L)	_	_	1.16 [0.87-1.55]	0.319	_	_

*HR = hazard ratio, CI = confidence interval, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention, VT = ventricular tachycardia. *significant at 5%*

Figure 1: Kaplan Mayer survival curves, overall (A), by gender (B), by presence and absence of monomorphic ventricular tachycardia (C), and by intubation status (D)



DISCUSSION

This is a single center retrospective observational study from the region with very limited research on ES. This study is important from many aspects. Firstly, it highlights a very important disease with very high mortality but very few options of successful treatment. Secondly, the data on ES is very scarce even internationally because most of the papers on this topic do not have enough number of patients so as to be able to generalize the results accurately. Thirdly, the research on this topic is not very robust in our country and thus we have very little understanding of the behavior of our patients with ES. Lastly and most importantly, due to the scarcity of resources in our country, the mortality assessment becomes more important due to non-availability of most modern and definitive treatment modalities for ES.

In our study, the commonest arrhythmia was monomorphic VT. This is in concordance with other studies where monomorphic VT has been shown to be the most common presentation of ES.[12] Monomorphic VT is mostly scar related whereas polymorphic VT is mainly because of ischemia. In ES, it is the scar related VT that is incessant and mostly resistant to intervention.

In our patients, IHD, severe LV dysfunction, DM, MR and TR were the main factors associated with ES. Prior research on this topic has also found, LV dysfunction and structural heart disease to be the major risk factors for ES.[13] Some of the studies have demonstrated the occurrence of VT storm in structurally normal heart like Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia.[14] Our study did not show the same because there was no representation of the channelopathies in our data. One reason might be

that our data was small as the occurrence of these channelopathies is very rare.

The most common presentation of our patients was pulmonary edema and cardiogenic shock associated with ES. This is because ES whether in the form of ventricular arrhythmias, or ICD shocks (whether appropriate or in appropriate) deteriorates the already compromised condition of the patients suffering from left ventricular dysfunction, Valvular heart disease or other structural heart disease. This is in accordance with previous studies where most of the patients have presented with pulmonary edema and cardiogenic shocks.[15] Such patients have very limited reserve if any of LV function and any small insult in the form of infection, drug non-compliance, ischemia or arrhythmia tips down the balance to deterioration, resulting in reduced cardiac output status and cardiogenic shock. Similarly, although appropriate ICD shocks are protective up to some extent, but repeated shocks lead to worsening of left ventricular function and de-compensation of patients. Same happened in our patients as well.

Multiple drugs were used in our patients, like, amiodarone, b-blockers and lidocaine, sedatives and antibiotics. These drugs have also been used in prior studies. Although the anti-arrhythmic drugs have no significant effect on all-cause mortality, their use in ES has been shown to be associated with short term reduction in both appropriate and inappropriate ICD shocks. That is the reason these drugs are an essential component of the management of ES.[10] As sympathetic over activity is both the initial trigger and the precipitating factor and has also an important role in the vicious circle of ES, the role of b-blockers in reducing sympathetic over activity both directly thru the beta 1 receptors and indirectly, through the central nervous system penetration and blockage of presynaptic adrenergic receptors cannot be overstated. Similarly amiodarone has got an established role in both the acute management and the prevention of recurrence of ES due to its multifaceted mechanism against cardiac arrhythmias. Lidocaine is an important pharmacological armamentarium against ES and is a recommended choice in Ventricular arrhythmias associated with acute myocardial infarction due to changes in myocardial membrane potential and pH. Sedation with benzodiazepines, propofol, opioid analgesics and general anesthetics are all essential in managing ES storm because these drugs reduce the sympathetic drive of such patients which is one of the main trigger and propagating factor for VA storm.[10, 16, 17]

The main short term intervention in our study was DC Cardioversion, with very negligible patients undergoing radiofrequency ablation (RA). The mortality of patients with ES storm varies in literature and is mainly dependent on the intervention that is executed. The main form of intervention that has shown both short and long term symptomatic benefits as well as the mortality benefits is RA. Literature shows that the average mortality is around 17% after successful RA of ES storm where as it is on the order of 42% in those with failed intervention or recurrence after RA.[18] Our data is completely in accordance with the literature as the mortality is our study is 40% because we did not offer RA to our patients and almost all of our patients were managed with sedation, intubation, pharmacological intervention and DC Cardioversion. This implies that the quality of care given to our patients with in the limited resources is appropriate but we need to direct attention and recourses to this devastating condition in terms of availability of latest treatment like RA so as to bring down our mortality to international figures.

As stated above, 60% of patients were discharged home in stable condition. The survival in our patients was inversely related with female gender, polymorphic ventricular tachycardia, baseline hemoglobin level and need for intubation. The need for intubation and high mortality in ES setting does not need explanation because it is the high risk patients who need intubation. Our study showed high mortality in female patients. Previous studies regarding this aspect show mixed results. Most show no gender difference in survival following ES although the occurrence of VT/VF is reported to be lower in women than in men.[19, 20] David. S and his colleagues have shown worse VT-free survival for women than men following ablation in their study which was conducted in 12- high volume centers.[21] Although our data is not robust to decide for sure on the basis of our study but in our set up, the limited resources and limited access of female population to health care facilities and medication might be one of the reasons why it is against the existing literature. Further studies must be done on this topic to better elucidate this point in our population as this will need our resources to be directed towards female population to reduce their mortality. Base line low hemoglobin/hematocrit level has previously been shown to be associated with high mortality in such patients.[22] The exact mechanism is unknown but one possibility may be that low hemoglobin level leads to increased oxygen demand on the heart from the body. The already compromised left

ventricular systolic function cannot support the high demand and thus deteriorated rapidly.

Limitations

Some limitation of our study must be acknowledged. It is a retrospective observational study. The no of patients is less and thus this must influence the interpretation of the results. The most definitive treatment of RA was offered to a very negligible no of patients and thus the outcome of our patients may not be representative of that in the developed world.

CONCLUSION

In conclusion, ES is a very serious condition but the mortality of our patients is comparable to the international figures for the conservative management. However modern therapies in the form of RA are required to be made available in various centers of our country for the better outcome of this disease. We have similar associated factors for VA storm like low EF and structure heart disease and thus we must pay attention to appropriate and timely management of heart failure and structural heart disease so that the ES burden and its mortality can be reduced.

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