Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/17045
DOI URL: http://dx.doi.org/10.21474/IJAR01/17045

ISSN NO. 2320-5407

RESEARCH ARTICLE

FACTORS ASSOCIATED WITH MORTALITY IN ADULT PATIENTS WITH SICKLE CELL DISEASE IN AL-AHSA, SAUDI ARABI, 2018-2022

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Manuscript Info

Manuscript History
Received: 05 April 2023
Final Accepted: 10 May 2023
Published: June 2023

Key words:-
Mortality, Adult Patients, Sickle cell Disease, Al-Ahsa, Saudi Arabi

Abstract

Sickle Cell Anemia is a genetic disorder caused by abnormal hemoglobin S production, leading to sickle-shaped red blood cells, anemia, and high morbidity and mortality rates. In Saudi Arabia, sickle-cell mutation affects 4.45% of the population, with a mortality rate of 0.73%. This case-controlled study aimed to identify mortality-associated factors among adults with Sickle Cell disease in Al-Ahsa from 2018 to 2022. Univariate analysis revealed several independent risk factors for mortality, such as gender, older age, chronic disease, SCD complications, previous surgery, CXR infiltration, and positive blood culture. Males exhibit a higher risk of non-survival compared to females, potentially due to more severe symptoms and complications. Older patients (>35 years) face an increased risk of non-survival due to age-related end-organ damage. Comorbidities, such as renal diseases and bronchial asthma, are prevalent in SCD patients and worsen with age. Lower hemoglobin levels, higher hospitalization frequency, and vaso-occlusive crises are associated with increased mortality rates. The study emphasizes the importance of comprehensive care, including specialist access, regular follow-up, and proper treatment, to improve survival outcomes. Early recognition and management of complications, such as renal failure and infection, along with interventions like vaccinations, prophylactic antibiotics, hydroxyurea, and splenectomy, can positively impact survival. Further research is needed to explore the underlying molecular mechanisms and develop more effective treatments for SCD.

Introduction:-

Sickle Cell Anemia is a autosomal recessive disorder that affects red blood cells, caused by production of abnormal hemoglobin S due to mutations on chromosome 11, resulting in high morbidity and mortality rates.(1,2) The number of people living with sickle cell disease in the United States is projected to be around 100,000 (3)

Malaria endemicity creates an enabling environment for sickle cell mutation carriers to thrive [4] Hemoglobin molecules cl[illegible]ts in blood cell rupture, anemia, p[illegible]om this disease [5,6].Usually, the si[illegible]evere conditions such as seizures, weakness in body parts, loss of consciousness, pulmonary hypertension, and speech problem in adults (7) It is crucial to point out that there is no cure of SCD except bone marrow transplant. However, treatment to relieve pain and prevent complications augment the patient's quality of life.(8)

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Sickle Cell Anemia was first reported in Saudi Arabia's Eastern provinces during the 1960s, affecting over 5% of the population, with a prevalence rate of up to 26% in the Southern and Eastern regions.(9) Sickle-cell mutation affects 4.45% of Saudi Arabia's population, with 0.26% having sickle-cell anemia, and the Eastern province has the highest incidence with 17% carrying the gene and 1.2% having sickle-cell syndrome,(10) making it a critical concern that requires more understanding of factors causing it and effective mitigation measures.

In the Eastern Province of Saudi Arabia, specifically in Al-Ahsa, sickle cell disease affects 1 out of every 80 people.(11) This disease is more common in tropical and subtropical regions. In Saudi Arabia, the disease can be either severe or benign, with a mortality rate of 0.73%. Most deaths occur among 20- to 30-year-olds, with 51.9% of them in this age group, and 20.7% among individuals younger than 20 years old.(11) The complexity of the factors causing Sickle Cell Anemia in Saudi Arabia makes identifying accurate mortality rates an uphill task.

According to the Cooperative Study of Sickle Cell Disease (CSSCD), the fatality rate among sickle cell disease (SCD) patients under 20 years old was 2.6%. However, mortality rates increased dramatically in adults (20-24 years old) from 0.6/100,000 to 1.4/100,000. Problems linked with the shift from pediatric to adult care can be the main reason for this increase.(12) Despite this unpredictability, investigating the risk factors of mortality among SCD patients is crucial to develop viable measures to reduce deaths and improve patients' well-being.

The study reviewed Sickle Cell Anemia patients in King Fahad Hospital, Al-Hofuf, Eastern Province, Saudi Arabia, and found that 77 out of 10,461 adult patients with Sickle Cell Anemia died during the study period. The male-to-female ratio was 1.3:1, with male participants had an average age of >30 years and females had a mean age of >27 years. The overall death rate was 0.73%, which is lower than the death rates recorded globally.(11) A cross-sectional study was conducted in four hospitals in the Jazan region of Saudi Arabia to evaluate the prevalence and characteristics of sickle cell patients admitted to medicine and pediatric wards between July 15 and August 15, 2018. The study found that sickle cell disease was the leading cause of hospitalization in Jazan hospitals, affecting one in every four patients. Female adults had the highest prevalence ratio of 50.1% compared to male patients at 49.5%. Most patients reported complications such as gallstones, vaso-occlusive crisis, acute chest syndrome, and stroke, with a mean age of 18.81±11.05.(10)

The rationale behind this study is to address the significant impact of sickle cell anemia on patients' quality of life, as it affects a large portion of the global population, with an estimated 300,000 infants born with the disease annually. The Middle East, particularly the Eastern Province of Saudi Arabia, has a high prevalence of sickle cell anemia, with 2% to 27% of individuals being carriers of the autosomal recessive mutation. Therefore, conducting this research in Al-Ahsa, Saudi Arabia, is essential in developing inferences based on rich data and predicting disease severity. By identifying the factors associated with adult mortality, actionable prevention strategies can be developed to decrease mortality rates and improve patients' quality of life through evidence-based symptomatic care. This study attempt to identify factors associated with mortality among hospitalized adults with Sickle Cell disease in Al-Ahsa from 2018 to 2022.

Materials and Methods:-

Study design, Setting and Participants

The current unmatched case control study was conducted at three healthcare facilities (i.e., King Fahad hospital, Prince Saud Bin Jalawy hospital, and Hereditary Blood Diseases Center) in Al Ahsa governorate, in the eastern region of the KSA from January 1, 2018 to December 31, 2022. During the study period, all adult patients (more than 18 years old) with confirmed diagnosis of sickle cell anemia were included in the study (n=183). The case group (61 subjects) was

defined as sickle cell disease patients who have died during hospitalization in the study period from January 2018 to December 2022. The control group (122 subjects) was defined as sickle cell disease patients who are still following up in the same hospitals that had an admission during the study period.

Sample size

The sample size was calculated using an online web-based calculator (openepi.com) [13]. The equation was built with a 95% confidence level, 80% power (% chanceof detecting), and (2:1) Ratio of Controls to Cases. The calculated sample size is (297). As the current study aims to identify the factors associated with mortality among SCA patients, the sample size will be proportional to (2:1) control-to-case ratio. To conclude, the study will include a total of (99) SCA patients who have died in the study period and (198) SCA patients who are alive and still following up in the same facility.

Data collection and analysis

The data collection sheet was developed based on the Literature review. The data collection sheet is composed of four sections; the first section collects sociodemographic data of the patients. The second section is concerned about the medical history of the patient, including comorbidities, previous attacks, and SCA complications [14]. The third section is concerned about laboratory investigation, including hemoglobin electrophoresis, complete blood counts and other biochemical parameters. The last section collects data about the outcome of the patients including death and its cause [15]. The mean and standard deviation were used for the descriptive analysis of metric variables, while frequencies and proportion (%) were given for categorical variables. Univariate analysis was conducted to determine the significant independent predictor of mortality among sickle cell disease patients with corresponding odds ratio and 95% confidence interval. All statistical analyses were performed using Statistical Packages for Software Sciences (SPSS) version 21, developed by IBM Corporation in Armonk, New York. Values were considered significant at a 95% confidence interval ($p<0.05$).

Ethical considerations

The present study was approved by Institutional Review Board in King Fahad hospital-hofuf in Al-Ahsa, eastern province, Saudi Arabia.

Results:-

This study was carried out on 183 patients with sickle cell disease; 61 represented cases (i.e., those who have died during hospitalization), and 122 represented controls (i.e., who are still following up in the same hospital).

In univariate analysis, independent risk factors for mortality rates include gender, older age, chronic disease, complication due to SCD, history of surgery, G6PD deficiency, CXF infiltration, and positive blood culture were the marginal risk factors for mortality rates. This further indicates that compared to the males, females were at increased risk of non-survival by at least 1.1-fold higher (OR=1.071; 95% CI=0.572 – 2.003; p0.831). Also, compared to the younger age group, older patients (> 35 years) were at increased risk of non-survival by at least 10.6-fold higher (OR=10.569; 95% CI=5.017 – 22.264; p<0.001). Moreover, patients with chronic disease were more likely at increased risk for mortality by at least 9.22 times higher than patients without the chronic disease (OR=9.22; 95% CI=4.159 – 20.438; p<0.001). Furthermore,patients who suffered complications due to SCD were predicted to increase the risk for mortality by at least 15.3 times higher (OR=15.353; 95% CI=4.559 – 51.704; p<0.001). In addition, patients with a previous history of surgery were predicted to increase the risk for mortality by at least 2.1-fold higher (OR=2.145; 95% CI=1.148 – 4.010; p=0.017). CXR infiltration patients were at increased risk for mortality by at least 29.5 times higher (OR=29.5; 95% CI=12.689 – 68.43; p<0.001), while those who had culture positive were at increased risk for mortality by at least 9.6 times higher (OR=9.620; 95% CI=3.033 – 30.513; p<0.001) [Table 1].

Table 1:- Risk factors for adult patients with sickle cell disease in Al-Ahsa, Saudi Arabia, 2018-2022.

Variable		Entire Sample (N=183)	Case (N=61)	Control (N=122)	Odds Ratio (95%CI)	P- value
		n (%)	n (%)	n (%)		
Gender	Male	110 (60.1%)	36 (59.0%)	74 (60.7%)	Reference	0.831
	Female	73 (39.9%)	25 (41.0%)	48 (39.3%)	1.071 (0.572 – 2.003)	

Age (years)	**≤35**	100 (54.6%)	12 (19.7%)	88 (72.1%)	Reference	**<0.001****
	>35	83 (45.4%)	49 (80.3%)	34 (27.9%)	10.569 (5.017 – 22.264)	
Chronic disease	**No**	84 (45.9%)	09 (14.8%)	75 (61.5%)	Reference	**<0.001****
	Yes	99 (54.1%)	52 (85.2%)	47 (38.5%)	9.220 (4.159 – 20.438)	
Complications due to SCD	**No**	57 (31.1%)	03 (04.9%)	54 (44.3%)	Reference	**<0.001****
	Yes	126 (68.9%)	58 (95.1%)	68 (55.7%)	15.353 (4.559 – 51.704)	
History of surgery	**No**	98 (53.6%)	25 (41.0%)	73 (59.8%)	Reference	**<0.017****
	Yes	85 (46.4%)	36 (59.0%)	49 (40.2%)	2.145 (1.148 – 4.010)	
G6PD deficiency	**No**	169 (92.3%)	55 (90.2%)	114 (93.4%)	Reference	
	Yes	14 (07.7%)	06 (09.8%)	08 (06.6%)	1.555 (0.514 – 4.700)	**0.434**
CXR infiltration	**No**	114 (62.3%)	10 (16.4%)	104 (85.2%)	Reference	**<0.001****
	Yes	69 (37.7%)	51 (83.6%)	18 (14.8%)	29.467 (12.689 – 68.43)	
Culture positive	**No**	164 (89.6%)	46 (75.4%)	118 (96.7%)	Reference	**<0.001****
	Yes	19 (10.4%)	15 (24.6%)	04 (03.3%)	9.620 (3.033 – 30.513)	

OR – Odds ratio; CI – Confidence Interval.
** Significant at p<0.05 level.

The median age of the cases group (49 years) was higher than that of the control group (28.5 years) in this study. However, the laboratory results of cases and control patients varied. It was found thatmedian Hgb S was higher in cases (81 gm/dL) than in the control group (75 gm/dL) with (OR=0.962; 95% CI=0.922 – 1.003; p=0.068). Also, median Hgb A was nearly equal in both cases and control groups (0 gm/dL) with (OR=1.09; 95% CI=0.976 – 1.218; p=0.127). Moreover, median Hgb A2 was higher in the cases' group (3 gm/dL) than in the control group (2.1 gm/dL) with (OR=0.935; 95% CI=0.718 – 1.219; p=0.62). On the other hand, median Hgb F was lower in the cases' group (16.6 gm/dL) than in the control group (21 gm/dL) with (OR=1.032; 95% CI=0.991 – 1.075; p=0.126). The white blood cells count in the cases' group (14,000/mL)] was higher than that of the control group(12,000/mL) with (OR=0.901; 95% CI=0.857 – 0.919; p=<0.001). However, the median Hgb level was lower in the cases' group (8 gm/dL) than in the control group (10 gm/dL) with (OR=1.411; 95% CI=1.188 – 1.677; p=<0.001). Likewise, the median platelets count was lower in the cases group (207,000/mcL) than in the control group (330,500/mcL) with (OR=1.003; 95% CI=1.001 – 1.005; p=<0.001). The median LDH level was higher in the blood of the cases' group (607 U/L) than that of the control group (411 U/L) with (OR=0.999; 95% CI=0.998 – 1.000; p=<0.001). As well, the median creatinine level was higher in the cases' group (108 micromoles/L) than that of the control group (54 micromoles/L) with (OR=0.990; 95% CI=0.984 – 0.995; p=<0.001). In addition, the median BUN level was higher in the cases' group (10.5 mg/dL) than that of the control group (4 mg/dL) with (OR=0.856; 95% CI=0.798 – 0.918; p=<0.001). Furthermore, the median T bilirubin level was higher in the cases' group (64.5 µmol/L) than that of the control group (52µmol/L) with (OR=0.995; 95% CI=0.991 – 0.998; p=0.005). Besides, the median D bilirubin level was higher in the cases' group (40 µmol/L) than that of the control group (12.8 µmol/L) with (OR=0.989; 95% CI=0.983 – 0.996; p=<0.001). Moreover, the median AST level was higher in the cases' group (57 U/L) than that of the control group (40 U/L) with (OR=0.999; 95% CI=0.997 – 1.001; p=0.192). Likewise, the median ALT level was higher in the cases' group (40 U/L) than that of the control group (31 U/L) with (OR=0.998; 95% CI=0.995 – 1.001; p=0.225). Independent risk factors for mortality rates also include frequency of hospitalization, ICU admission, vaso-occlusive crisis, and blood transfusion. This further indicates increasing frequency of hospitalization (OR=1.266; 95% CI=1.086 – 1.476; p=0.003), vaso-occlusive crisis (OR=1.420; 95% CI=1.231 – 1.637; p=<0.001) and blood transfusion (OR=1.025; 95% CI=0.838 – 1.253; p=0.812) in control group. However, there was an increased frequency of ICU admission inthe cases' group (OR=0.757; 95% CI=0.552 – 1.037; p=0.083). [Table 2].

Table 2:- Median, the mean difference between dead (cases) and alive (control) adult patients with sickle cell disease in Al-Ahsa, Saudi Arabi 2018-2022.

Variable	**Normal reference**	**Case**		**Control**			
		Median	**Mean ± SD**	**Median**	**Mean ± SD**	**Odds Ratio (95%CI)**	**P-value**
Age (in years)		49	47.52 ± 14.61	28.5	31.41 ± 11.49		
Hgb S(gm/dL)		81	79.16 ± 5.46	75	72.10 ± 9.70	0.962 (0.922 –	0.068

						1.003)	
Hgb A(gm/dL)		0	0.04 ± 0.34	0	0.34 ± 2.32	1.090 (0.976 – 1.218)	0.127
Hgb A2(gm/dL)		3	3.13 ± 0.78	2.1	2.38 ± 0.86	0.935 (0.718 – 1.219)	0.62
Hgb F(gm/dL)		16.6	17.28 ± 9.07	21	21.25 ± 7.57	1.032 (0.991 – 1.075)	0.126
WBC (1000/mL)	(4-11)	14	16.70 ± 12.20	12	12.94 ± 5.53	0.901 (0.857 – 0.919)	**<0.001 ****
Hgb (gm/dL)	(12-18)	8	7.82 ± 1.83	10	9.58 ± 1.83	1.411 (1.188 – 1.677)	**<0.001 ****
Platelets (1000/mcL)	(150-400)	207	249.36 ± 207.96	330.5	355.77 ± 198.55	1.003 (1.001 – 1.005)	**0.002 ****
LDH (U/L)	(140-280)	607	1487.72 ± 2665.45	411	492.24 ± 338.48	0.999 (0.998 – 1.000)	**0.008 ****
Creatinine (micromoles/L)	(52-115)	108	152.70 ± 155.74	54	68.10 ± 80.44	0.990 (0.984 – 0.995)	**<0.001 ****
BUN (mg/dL)	(7-20)	10.5	12.32 ± 9.16)	4	4.85 ± 3.65	0.856 (0.798 – 0.918)	**<0.001 ****
T bilirubin (µmol/L)	(< 20)	64.5	121.22 ± 156.36	52	71.23 ± 67.09	0.995 (0.991 – 0.998)	**0.005 ****
D bilirubin (µmol/L)	(< 5.1)	40	76.37 ± 90.99	12.8	34.90 ± 57.74	0.989 (0.983 – 0.996)	**0.001 ****
AST (U/L)	(< 33 U/L)	57	118.80 ± 160.80	40	56.31 ± 78.56	0.999 (0.997 – 1.001)	0.192
ALT (U/L)	(< 37 U/L)	40	74 ± 147.13	31	53.54 ± 92.86	0.998 (0.995 – 1.001)	0.225
# of Hospital admission	0	2.4	2.46 ± 2.19	4.3	4.36 ± 4.60	1.266 (1.086 – 1.476)	**0.003 ****
# of ICU admission	0	2.8	1.03 ± 0.58	1.5	0.77 ± 1.09	0.757 (0.552 – 1.037)	0.083
# of Vaso occlusive crisis	0	3.1	3.10 ± 2.43	7.8	9.15 ± 8.49	1.420 (1.231 – 1.637)	**<0.001 ****
# of Blood transfusion	0	1.6	2.07 ± 1.85	2.9	2.14 ± 1.69	1.025 (0.838 – 1.253)	0.812

OR – Odds ratio; CI – Confidence Interval.

** Significant at p<0.05 level.

Multivariable Cox regression was performed using age as the timescale to identify the survival time for chronic diseases associated with sickle cell disease. The hazard ratio (HR=39756.922) in renal diseases was very high (95% CI=0.000 – 322.972; p=0.312). This ratio is followed by bronchial asthma (HR=9615.549; 95% CI=0.000 – 29.06; p=0.228). Also, malignancy has a high hazard ratio (HR=1891.92; 95% CI=0.000 – 1860.533; p=0.194). This is followed by other chronic diseases (HR=223.646; 95% CI=0.787 – 63.391; p=0.057). Hypertension has (HR=10.301; 95% CI=0.000– 38.22; p=0.763). Moreover, neurological diseases have (HR=4.740; 95% CI=0.000– 1.730; p=0.767). Less hazard ratio (HR=1.990) was found in diabetes with (95% CI=0.000 – 95.62; p=0.900), in cardiovascular diseases (HR=0.001; 95% CI=0.000– 154.618; p=0.265) and in immunological diseases (HR=0.000; 95% CI=0.000– 620.928; p=0.302). [Table 3].

The presence of complications of sickle cell disease has a hazard ratio. This hazard ratio is manifested especially in renal failure (HR=11.603; 95% CI=0.000– 36.02; p=0.642) and in infection (HR=5.455; 95% CI=0.000– 24.427; p=0.798) followed by sepsis (HR=1.037; 95% CI=0.000– 367.367; p=0.996). Other complications, including hepatic crisis, stroke, hemolytic reactions, acute chest syndrome, pulmonary hypertension, and splenomegaly, have no hazard ratio.Moreover, the drugs used have no hazard ratio [Table 3].

Table 3:- Cox Regression Analysis of Variables Associated with Survival for Subjects with sickle cell disease in Al-Ahsa, Saudi Arabi 2018-2022.

Variable (a)		Hazard ratio(HR)	95% Confidence Interval (CI)		P-value
			Lower	Upper	
Chronic diseases	Hypertension	10.301	0.000	38.22	0.763
	Diabetes	1.990	0.000	95.62	0.900
	Bronchial asthma	9615.549	0.003	29.06	0.228
	Cardiovascular disease	0.001	0.000	154.618	0.265
	Renal disease	39756.922	0.000	322.972	0.312
	Immunological disease	0.000	0.000	620.928	0.302
	Liver diseases	117.829	0.000	239.717	0.694
	Malignancy	1891.92	0.000	1860.533	0.194
	Neurological disease	4.740	0.000	1.730	0.767
	Another chronic disease	223.646	0.787	63.391	0.057
Sickle cell disease complications	No complications	0.049	0.000	17.618	0.644
	Renal failure	11.603	0.000	36.02	0.642
	Sepsis	1.037	0.000	367.367	0.996
	Infection	5.455	0.000	24.427	0.798
	Hepatic crisis	0.000	0.000	786.194	0.282
	Stroke	0.005	0.000	283.83	0.561
	Hemolytic reaction	0.002	0.000	31.202	0.211
	Acute chest syndrome	0.224	0.000	88.6	0.371
	Pulmonary hypertension	0.007	0.000	321.982	0.365
	Splenomegaly	0.009	0.000	352.457	0.384
	Other	0.000	0.000	1.28	0.425
Drugs used	Vit D	0.840	0.840	0.840	0.840
	Antibiotics	0.840	0.840	0.840	0.840
	Aspirin	0.308	0.308	0.308	0.308
	Hydroxyurea	0.932	0.932	0.932	0.932
	Antiviral	0.869	0.869	0.869	0.869
	Analgesics	0.423	0.423	0.423	0.423
	Folic acid	0.064	0.064	0.064	0.064
	Tramadol	0.870	0.870	0.870	0.870
	Others	0.662	0.662	0.662	0.662
	No treatment	0.982	0.982	0.982	0.982

Input variables[a]: chronic diseases, sickle cell disease complications, and drug use. The input variables were selected based on univariate analysis results, whether they were associated with mortality or not. The final model is shown in the table and is obtained through backward stepwise model selection if they were significant at the 0.10 level. The hazard ratio units represent an increase per one-unit change of the factor.

This study found that no CXR infiltration has a higher survival possibility than unilateral then bilateral infiltration (Fig.1a). Also, the use of hydroxyurea has higher survival possibility (Fig.1b). Moreover, the absence of septic shock has a higher survival possibility than its absence (Fig.1c). Furthermore, splenectomy has higher survival possibility.

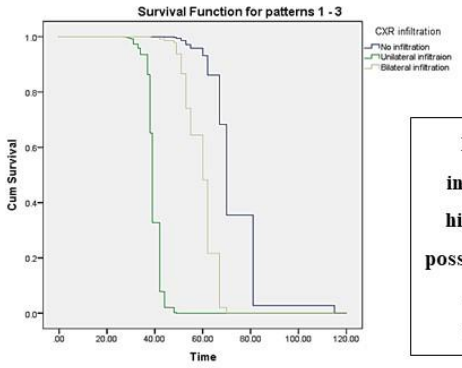

Fig 1a: No CXR infiltration has higher survival possibility than uni- & bilateral infiltration

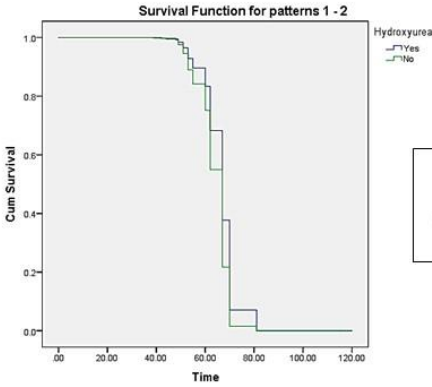

Fig. 1b:Hydroxyurea treatment has higher survival possibility than no use

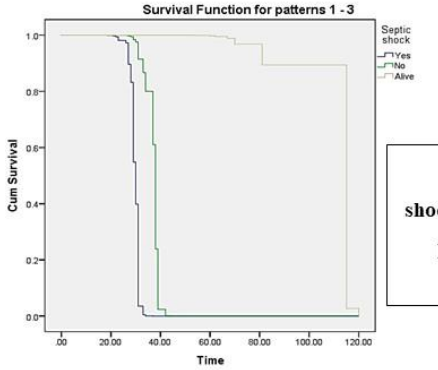

Fig 1c: No septic shock has higher survival possibility than its presence

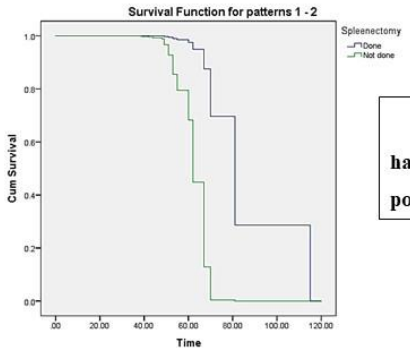

Fig. 1d: Splenectomy has higher survival possibility

Discussion:-

This case controlled study shows that several factors are associated with the mortality in adult patients with sickle cell disease. In terms of mortality (33.3%), theresults of this study are consistent with the previous studies. A retrospective study conducted by Alabdulaaly et al. and Al-Suliman et al. reported a mortality rate of 30% and 27% respectively, among adult patients with Sickle cell disease (SCD).[16,17] According to a study by Gardner et al., patients with sickle cell disease have a death rate of 12.4%.[18] This is much lower compared to the current study's mortality rate of 33.3%. Another study by Ballas et al. found that the mean frequency of hospital admissions in sickle cell disease patients was 1.7 per year, which is lower than the mean frequency of hospital admissions found in the current study (3.74 per year).[19]

In the univariate analysis, several independent risk factors that significantly influenced mortality rates were identified. Gender emerged as a significant predictor, with males at an increased risk of non-survival compared to females. This finding is consistent with previous research showing that males with SCD often experience more severe symptoms and higher rates of complications, leading to poorer outcomes.(20) Gender differences in adult SCD patients have been linked to sex hormones.(21)Nitric oxide is hypothesized to play a role in maintaining vasomotor tone, preventing platelet aggregation, reducing the risk of injury from ischemia-reperfusion, and controlling the expression of endothelial adhesion molecules.(22)Estrogens facilitate the synthesis of nitric oxide while reducing its consumption. Since nitric oxide is known to be higher in the female population. Male patients with sickle cell anemia may benefit the most from treatments that enhance non-nitric oxide driven vasodilatation, reduce nitric oxide consumption, or restore nitric oxide bioactivity.(23)

Age was also a significant risk factor, with older patients (>35 years) facing a substantially higher risk of non-survival. This observation aligns with previous studies highlighting the impact of age on SCD prognosis and the increased risk of complications associated with aging. As SCD patients get older, they begin manifesting signs of end-organ damage, which increases morbidity and mortality.An analysis conducted by the Cooperative Study of Sickle Cell Disease revealed the median age of death was 48 years for women and 42 for men.(20)Recently, the National Center for Health statistics published population-based surveillance data for all causes of death among 12 000 patients with SCD. The overall age of

death was 43 years for females and 40 years for males.(24)The reason is that the majority of adult sickle cell patients suffer from CNS injury(25) and chronic renal failure(26) that progresses with age.

Our study revealed substantial proportion of patientshad comorbidities such as renal diseases, bronchial asthma, malignancy, and other chronic conditionswhich is consistent with previous studies.[27] There are many co-morbidities associated with SCD, which worsen with age and can impair almost any organ system in the body. Acute comorbidities include acute chest syndrome (ACS),vaso-occlusive crisis, stroke, acute renal failure, splenic sequestration, priapism, hepatobiliary complications and acute ocular conditions; these can occur at any age. Chronic comorbidities such as avascular necrosis (AVN), pulmonary hypertension (PH), leg ulcers,diastolic heart dysfunction, gout, end-stage renal disease (ESRD) and ophthalmologic complications increase with age.[28]Hypertension in SCD patients may be due to several factors, including renal impairment, endothelial dysfunction, and increased vascular stiffness, and is associated with increased morbidity and mortality.[29]

The risk of early death is highest among patients who have had severe complications, such as renal failure, underlying infection or sepsis.Polymerization and red cell sickling which ultimately leads to glomerular malfunction manifested initially as proteinuria and potentially progressing to chronic renal failure.[30]

This is in contrast to the study conducted by Al-Jaouni et al. (2015) on 260 sickle cell disease patients which shows the most common complications were bone pain crisis (70.3%), ACS (23.8%), and stroke (5.9%).[31] Hemolysis with the subsequent release of cell-free hemoglobin results in the generation of reactive oxygen species which is a potent scavenger of nitric oxide.[32] This appears to predispose patients to a vasculopathy, characterized by systemic and pulmonary hypertension, endothelial dysfunction, and proliferative changes in the intima and smooth muscle of blood vessels[33] may lead to ACS.

Septic shock is a life-threatening complication of infections, and SCD patients are particularly susceptible to infections due to their immunocompromised state.[34] In our study, the second most common cause of mortality was septic shock (49.2%), which is similar to previous studies.[12] This is in contrast to the study conducted in Jamaica which found that male gender and a history of stroke were associated with increased mortality in SCD patients.[35] Sickle cell patients have a known predisposition to bacterial infection, particularly pneumococcal infection.[36,37] Bacteria could also superinfect an area of ischemic lung tissue. For these reasons, the ACS is almost always treated with antibiotics.[36,37] which supports the evidence that antibiotics are taken by most of the patients in our study. To reduce the risk of infections, SCD patients should receive routine vaccinations and prophylactic antibiotics as appropriate.[38]Hydroxyurea reduces some vaso-occlusive complications of SCA.[39] While its mechanism of action is incompletely understood, hydroxyurea is associated with increased levels of HbF in SCA; increased levels of HbF are known to improve survival.[20]Spleenectomy in patients with SCD is also beneficial in reducing their transfusion requirements and its attendant risks, eliminating the discomfort from mechanical pressure of the enlarged spleen, avoiding the risks of ASSC, and managing splenic abscess.[40] But there is a growing concern about overwhelming postspleenectomy sepsis which is certainly a hazard.[41]

The analysis of laboratory parameters revealed several factors that were significantly associated with mortality rates. Lower Hgb levels were found to be a predictor of increased mortality risk, indicating the importance of monitoring and managing anemia in SCD patients because higher Hb levels are associated with a reduced risk of developing end organ damage.[42] Hospitalization frequency and vaso-occlusive crisis were significantly associated with increased mortality rates, suggesting that VOCis the primary reason for hospitalizations in SCD patients and is linked to higher death rates and organ damage.[43] Interestingly, ICU admission seemed to be associated with lower mortality rates. As there is very little in the literature on ICU patients with SCD, we have no statistics to compare. But general medical logic tells us that we can lower this rate by earlier critical care interventions in ICU.[44]

Hence, this study identified several independent risk factors for mortality in patients with sickle cell disease. The mortality rates observed in this study and previous studies in Saudi Arabia are likely due to the lack of comprehensive care for SCD patients, including access to specialist care, regular follow-up, and adequate treatment. The Saudi Ministry of Health has acknowledged the need to improve the quality of care for SCD patients and has launched a national program to improve the management of the disease. We believe that this study will provide better insights for understanding factors responsible formortality of the patients with SCD and measures to prevent morbidity and mortality in such patients.

Limitations

Selection bias may be present as only patients admitted to Al-Ahsa hospitals were included in the study. Patients who were managed in other healthcare facilities were not included, and thus the findings may not be generalizable to the wider population.The study design, being a retrospective case-control study, is limited by the quality and completeness of the medical records available. There may be missing data or inaccuracies in the documentation, which could lead to incorrect conclusions.

Conclusion:-

In conclusion, this study provides valuable insights into the risk factors and prognostic indicators associated with mortality in patients with sickle cell disease (SCD). The findings highlight the importance of considering various demographic, clinical, and laboratory parameters when assessing the survival outcomes of individuals with SCD.Furthermore, the study highlights the significance of early recognition and management of complications associated with SCD, such as renal failure, infection, and sepsis. Timely interventions, including routine vaccinations, prophylactic antibiotics, use of hydroxyurea and splenectomy, have demonstrated a positive impact on survival outcomes in SCD patients. This study adds valuable insights to the existing literature and provides crucial guidance to clinicians and researchers in the field. Further research is needed to explore the underlying molecular and genetic mechanisms of SCD and to develop more effective treatments.

Acknowledgement:-

The authors would like to acknowledge the cooperation of allhospitals medical records administration during the conduct of this study. Special thanks to those who helped with data collection for the study.

Conflict of interest

The authors declare no conflict of interest.

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