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Original Research Article

Outcomes and Clincopathological Features of Advanced Cancer Patients Admitted to Intensive Care Unit with Different Acute Presentation Patterns

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Abstract

The study evaluates the most common acute presentation patterns of cancer patients, and correlation to clinicopathological features. Of 324 patients, 60.8% are male with mean age was 60.5 year, and mean length of ICU stay is 3-days. 44.4% of patients transferred to Medical Unit, while 55.6% patients died during ICU admission. The most common cause of ICU admission in cancer patients is acute respiratory symptoms, followed by cardiovascular symptoms. The most common cancer is lung cancer, followed by GIT and hematological cancers .The study has found a significant relation between the acute presentations and the type of cancers (p=0.02), outcome (p=0.01), and length of ICU stay (p=0.05). Patients admitted from Oncology units were associated with more female patients, better outcome (p<0.0001), and longer mean ICU stay (3-days) than patients who direct admitted from home. Univariate tests revealed that male gender, older age, specific cancer such as melanoma and sarcoma, and direct admissions from home were associated with high mortality rate in the IC. Accurate diagnosis and appropriate treatment of cancer-related problems such as pain management, and rehydration might be highly recommended to reduce a number of patient that need real ICU services.

Keywords

Acute presentation

Advanced cancer

Clinicopathological features

Intensive care unit

Introduction

Oncologic emergencies can occur at any time during the course of a malignancy, from the early diagnostic features to the end-stage disease. However, patients with advanced cancer are often admitted to the hospital as emergency cases. This may not always be medically emergency (Walji et al., 2008; Behl et al., 2010; Longo et al., 2012). Emergencies in the cancer patients may be classified into three categories: effects from tumor progression, metabolic or hormonal effects mediated by tumor products, and treatment complications. It is well known that the recurrent admissions to the intensive care unit (ICU) are important indicators during end-of-life care. Presence of a well-developed home, and inpatient specialist palliative care provide a significantly improvement in symptoms control, and reduced hospital admissions (Longo et al., 2012; DeVita, 2011; Paci et al., 2001). Today, modern multimodal therapies have significantly improved the cancer survival

(Kreftregisteret, 2011; Verdecchia et al., 2007). This emphasizes the need for best management and maintenance of quality of life throughout the disease progression; patients with advanced cancer frequently experience worsening symptoms, physiological deterioration, and emotional distress. Many of these patients require palliative care for symptom management, psychosocial support and transition to the end of life palliative care needs professional and skillful teamwork and close collaborations with oncologist to provide comprehensive cancer care (Kreftregisteret, 2011; Smith et al., 2012; Bruera and Hui, 2010 Earle et al., 2003; Yates and Barrett, 2009; Barbera et al., 2010).

The aims of current study are to evaluate the most common tumor associated with acute presentations, to characterize common patterns of clinical emergencies at our institution. In addition, assess the interventions performed during ICU hospitalization.

To our knowledge, such study on the outcome of ICU cancer centers in Libya has not been published previously. In this concerning, a better understanding of the factors associated with ICU admissions would allow clinicians to distinguish patients who are appropriate for only primary health care from those who need admission in the ICU.

Patients and Methods

Subjects

This retrospective study was conducted on 324 patients. All patients admitted and treated in ICU of Misurata cancer center between January 1, 2012 and December 31, 2013 were included in current study. The Misurata Cancer Center is a 160-bed teaching hospital; it had an 8-bed ICU to serve patients with advanced cancer. The ICU prepared by multidisciplinary staff of medical ICU specialists, physicians, nurses, physiotherapists, and pharmacists. The clinical data regarding characteristics of patients were collected from patients' files during hospitalization that included an ICU stay, clinical features such as (sex, age at presentation, cancer diagnosis, stage, referred doctor or place, type of emergency at time of presentation, duration of admission, different type of treatment, discharge outcomes and ICU follow-up of the patient). Patients were daily followed-up until they died or to the discharged time from hospital. In this study, in addition to patients transferred from oncology units (booked patient); we included patients directly admitted from home (un-booked patients).

Statistical analyses

The statistical analyses were performed using SPSS software packages for Windows, versions 19.0 (SPSS, Inc., Chicago, USA). The variables of the material were grouped into logical classes and descriptive statistics calculated for the continuous variables. For ICU survival analysis, Kaplan-Meier curves were plotted, and differences between the curves analyzed using the log-rank test. ICU survival time was calculated from the time of ICU admission to the date of death from any cause or that date at which the patient was discharged from ICU or at the date of last known ICU follow-up. To identify factors on ICU admission associated with death, we compared the baseline and admission characteristics between patients who died at the end of ICU admission to those who were discharged alive from ICU. Comparisons were made using the Student's t test for continuous variables that were normally distributed (i.e., age), the Mann-Whitney test for continuous, nonparametric variables (e.g., admission length), and Pearson's test for categorical variables (e.g., gender, years of admission). Pearson and Spearman's correlation tests were used for comparison between two variables. P-values below 0.05 were regarded as significant. Comparison of numerical data was done by the chi-square test. Student t-tests and ANOVA were also used to test differences between the groups. Univariate and multivariate analyses were performed for all studied prognostic features to estimate their effect on disease outcome, together or separately. Microsoft Excel 2007 was used to draw graphs and to evaluate relationships between variables.

Results

The characteristics of the 324 patients who required admission to the ICU during the study period are shown in Table 1 .A retrospective study of 197 (60.8%) males of mean age 64.4 ± 17.7 years (range 9-98 years) and 127 (39.2%) females of mean age 54.5 ± 16.6 years (range 14-95 years) having advanced cancer were admitted to ICU by acute presentation.

Fig. 1 shows the most frequent indications of oncology emergency admission to the ICU, which including respiratory symptoms such as dyspnea, pleural effusion, pneumonia, embolism in 87 (26.9%). Followed by

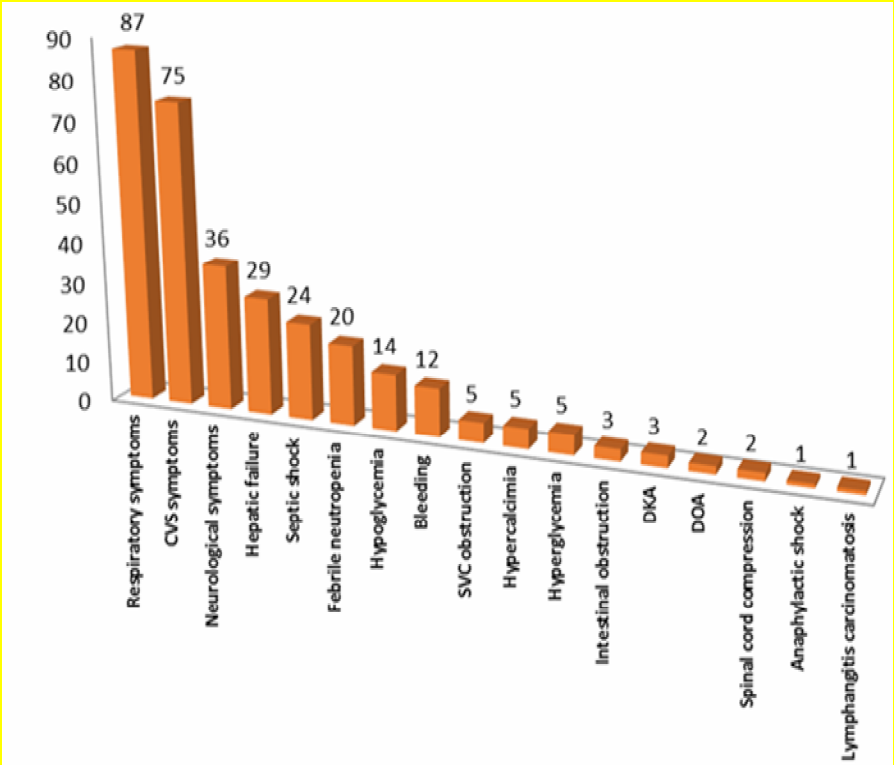
cardiovascular symptoms such as arrhythmia, ischemic pain and dyspnea in 75 (23.1%), neurological symptoms such severe pain in 36 patients (11.1%), gastrointestinal symptoms such as nausea, vomiting and hepatic coma in 29 patients (9.0%), and septic shock and febrile neutropenia without shock (in 24 and 20 patients respectively).

Table 1. Characteristics of 324 patients admitted to ICU.

Characteristics		No.	Percent
Sex	Male	197	60.8
	Female	127	39.2
Admission type	Transfers to ICU from oncology unit	300	92.6
	Direct admission to IAPCU	24	7.4
Diagnoses of cancer			
	Lung cancer	77	23.8
	*GIT cancer	45	13.9
	Biliary system pancreatic duct cancer	36	11.1
	‡hematolymphatic(Leukemia & lymphoma)	36	11.1
	Gynecologic cancer	26	8.0
	Breast cancer	25	7.7
	Malignant brain tumors	17	5.2
	Nasopharyngeal carcinoma	16	4.9
	Prostatic cancer	16	4.9
	Renal cancer	10	3.1
	Hepatocellular carcinoma	5	1.5
	Sarcomas	4	1.2
	Thyroid cancer	4	1.2
	Skin melanoma and squamous carcinoma	4	1.2
	Multiple-myeloma	1	0.3
	Parotid cancer	1	0.3
	Unknown primary	1	0.3
Acute presentation			
	Respiratory symptoms	87	26.9
	ºCVS symptoms	75	23.1
	Neurological symptoms	36	11.1
	Hepatic failure	29	9.0
	Septic shock	24	7.4
	Febrile neutropenia	20	6.2
	Hypoglycemia	14	4.3
	Bleeding	12	3.7
	SVC obstruction	5	1.5
	Hypercalcemia	5	1.5
	Hyperglycemia	5	1.5
	Intestinal obstruction	3	0.9
	§ DKA	3	0.9
	□ DOA	2	0.6
	Spinal cord compression	2	0.6
	Anaphylactic shock	1	0.3
	Lymphangitis carcinomatosis	1	0.3
ICU Outcome	Alive	144	44.4
	Dead	180	55.6
		Mean	Range
Age		60.5	9-98
Length of stay in ICU in days		2.7	1-22

GIT cancer = gastrointestinal tract: colon (n 27), gastric (n 13), anal (n 3), esophagus (n 1), small bowel cancer patients (n 1),‡ hematolymphatic:lymphoma (n 17), leukemia (n 19),
ºCVS=Cardio Vascular System, §DKA =Diabetic ketoacidosis), □DOA = Dead on Admission.

Fig. 1: Most frequent acute presentations that are indicators for emergency admissions.



In our study, 300 patients (92.6%) have booked registration cases; were transferred from oncology units, whereas 24 patients (7.4%) are directly received from home (un-booked registration); 20 of them are unknown cancer patient. Those were clinically diagnosed as cancer patients during an emergency admission, after that the Acute patterns of cancer patients that admitted to the ICU were more frequent in male patients (61.0%) than in female patients (39.0%) at univariate analysis, with statistical significance (p=0.01). Men have more than 70% of respiratory, neurological symptoms and superior vein cava (SVC) obstruction. In addition, five patients with hypercalcemia, patient with anaphylactic shock presentations and two patients died on admission time were also all men (Table 2).

The most frequent primary cancer sites are the lung 77 (23.8%), the gastrointestinal tract 45 (13.9%), pancreatic and biliary duct 36 (11.1%) hematolymphoid tissue 36 (11.1%) and the gynecological and breast cancers (8.0% and 7.7% respectively) (Table 1).

Interestingly, the study shows a significant relation between the acute presentations and the type of cancers (p=0.02). The majority of patients have respiratory, cardiac or neurological symptoms, for example, the majority of patients with respiratory symptoms have seen in lung cancer (52.9%), followed by nasopharyngeal carcinoma (10.3%), breast cancer (9.2%), gynecological cancers (6.9%), colon cancer (3.4%), and brain cancer (3.4%). Tendency to bleeding are usually seen in GIT tumors. Whereas, majority of patients complaining of fever with or without septic shock, they have either leukemia or lymphoma, and patients complaining of hypercalcemia, they have either prostatic cancer or lung cancer.

In general, we have found that the mean length of hospital ICU stay was 2.7 days (range 1-22). The ICU staying for 166 (51.2%) patients was 1 day. On other hand, approximately 204 (63.0%) patients are admitted to ICU with length of stay below the mean, whereas 180 (55.6%) patients are died during their ICU hospitalization, they have mean staying of 2.4 days (range 1-15)

Current study also compare between booked patient (admitted from Oncology units) and non-booked patients (direct admitted from home). The result shows that booked patients are relatively associated with more female patients (121 to 6 patients in non-booked patients), better outcome (p<0.0001), and longer mean ICU stay (3-days).Whereas, non-booked patients are associated with high mortality rate in the ICU.

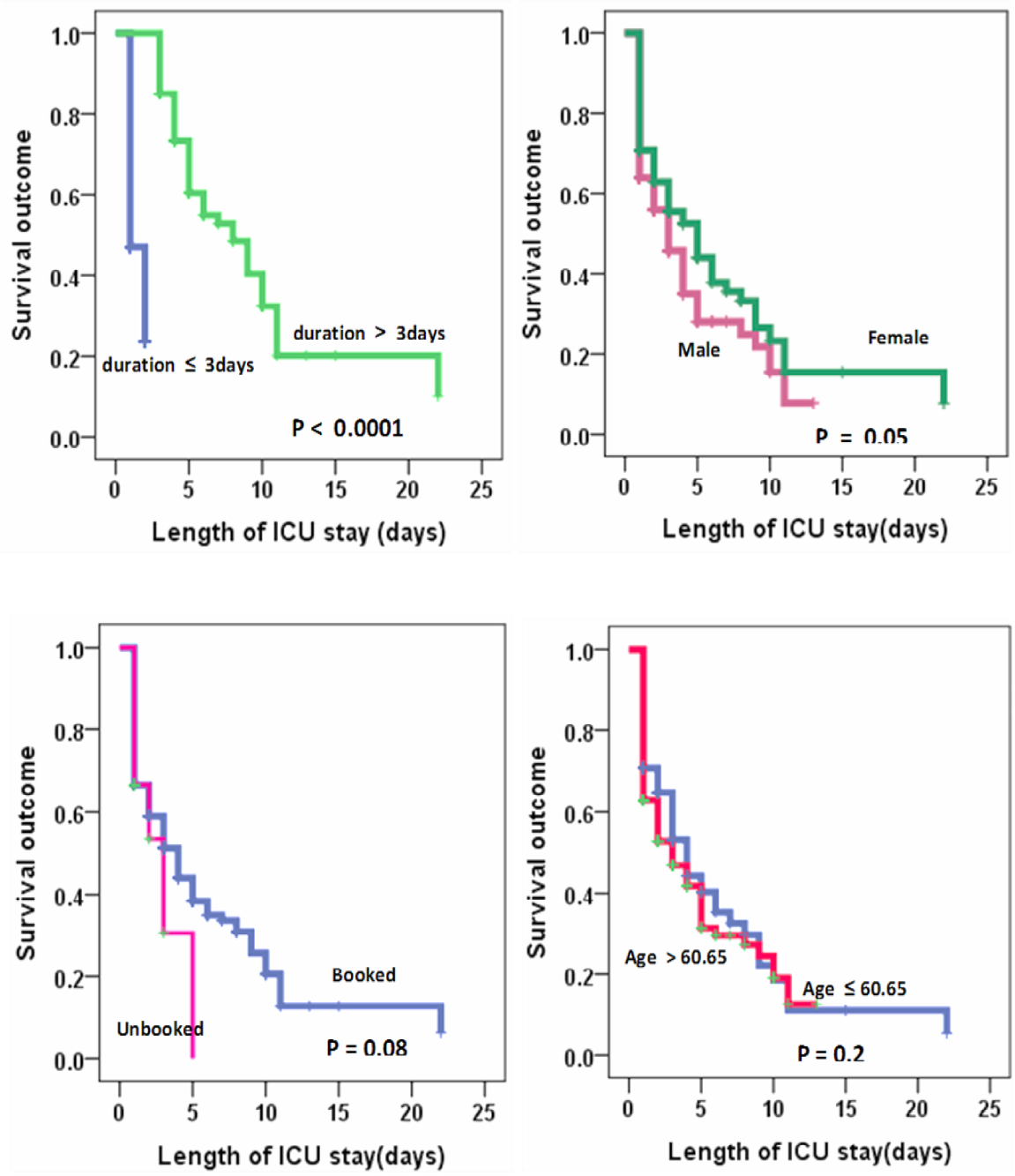
Table 2. Factors correlated with gender and registration type.

Characteristics		Gender		*p*-value	Registration		*p*-value
		Male (no.)	Female (no.)		Booked (no.)	Non-booked (no.)	
Age	Above the mean	123	44	<0.0001	152	15	0.18
	Below the mean	74	83		148	9	
Diagnoses of cancer							
Lung cancer		70	7	<0.0001	70	7	0.79
GIT cancer		22	23		43	2	
Gallbladder and biliary pancreatic duct cancer		21	15		31	5	
Leukemia and lymphoma		19	17		35	1	
Gynecologic cancer		0	26		24	2	
Breast cancer		3	22		24	1	
Malignant brain tumors		16	1		15	2	
Nasopharyngeal carcinoma		11	5		15	1	
Prostatic cancer		16	0		16	0	
Renal cancer		8	2		9	1	
Hepatocellular carcinoma		4	1		4	1	
Sarcomas		2	2		4	0	
Thyroid cancer		1	3		4	0	
Skin Melanoma and Squamous carcinoma		4	0		3	1	
Multiple-myeloma		0	1		1	0	
Parotid cancer		0	1		1	0	
Unknown primary		0	1		1	0	
Acute presentation							
Respiratory symptoms		63	24	0.01	79	8	0.62
CVS symptoms		36	39		72	3	
Neurological symptoms		26	10		32	4	
Hepatic failure		17	12		25	4	
Septic shock		9	15		23	1	
Febrile neutropenia		10	10		19	1	
Hypoglycemia		9	5		13	1	
Bleeding		9	3		12	0	
SVC obstruction		4	1		4	1	
Hypercalcimia		5	0		5	0	
Hyperglycemia		3	2		5	0	
Intestinal obstruction		0	3		3	0	
DKA		2	1		3	0	
DOA		2	0		1	1	
Spinal cord compression		1	1		2	0	
Anaphylactic shock		1	0		1	0	
Lymphangitiscarcinomatosis		0	1		1	0	
ICU admission Outcome	Alive	87	57	0.49	136	8	0.18
	Dead	110	70		164	16	
Year of admission	2012	97	55	0.31	139	13	0.53
	2013	100	72		161	11	
Length of stay in ICU in days							
Above the mean		61	59	0.005	113	7	0.41
Below the mean		136	68		187	17	

Table 3. Factors associated with death in ICU.

Characteristics	Outcome				*p*-value
	Alive		Dead		
	No.	%	No.	%	
Age					
> 60.5 years	70		83		0.35
≤ 60.5 years	74		97		
Diagnoses of cancer					
Lung cancer	35	45.5	42	54.5	0.02
GIT cancer	18	40.0	27	60.0	
Gallbladder & biliary pancreatic duct cancer	15	41.7	21	58.3	
Leukemias and lymphoma	12	33.3	24	66.7	
Gynecologic cancer	15	57.7	11	42.3	
Breast cancer	11	44.0	14	56.0	
Malignant brain tumors	12	70.6	5	29.4	
Nasopharyngeal carcinoma	7	43.8	9	56.3	
Prostatic cancer	9	56.3	7	43.8	
Renal cancer	2	20.0	8	80.0	
Hepatocellular carcinoma	1	20.0	4	80.0	
Sarcomas	1	25.0	3	75.0	
Thyroid cancer	2	50.0	2	50.0	
Skin Melanoma and Squamous carcinoma	1	25.0	3	75.0	
Multiple-myeloma	1	100.0	0	0	
Parotid cancer	1	100.0	0	0	
Unknown primary	1	100.0	0	0	
Acute presentation					
Respiratory symptoms	35	40.2	52	59.8	<0.0001
CVS symptoms	33	44.0	42	56.0	
Neurological symptoms	26	72.2	10	27.8	
Hepatic failure	3	10.3	26	89.7	
Septic shock	1	4.2	23	95.8	
Febrile neutropenia	8	40.0	12	60.0	
Hypoglycemia	12	85.7	2	14.3	
Bleeding	8	66.7	4	33.3	
SVC obstruction	3	60.0	2	40.0	
Hypercalcemia	3	60.0	2	40.0	
Hyperglycemia	5	100.0	0	0	
Intestinal obstruction	2	66.7	1	33.3	
DKA	2	66.7	1	33.3	
DOA	0	0	2	100.0	
Spinal cord compression	2	100.0	0	0	
Anaphylactic shock	1	100.0	0	0	
Lymphangitiscarcinomatosis	0	0	1	100.0	
Registration					
Booked	136	45.3	164	54.7	0.18
Non-booked	8	33.3	16	66.7	
Year of admission					
2012	78	51.3	74	48.7	0.01
2013	66	38.4	106	61.6	
Length of stay in ICU in days					
Above the mean	67	55.8	53	44.2	0.001
Below the mean	77	37.7	127	62.3	

Fig. 2: Outcome of ICU patients according to clincopathological features in advanced cancer patients admitted to ICU.
A. Survival curves based on length of ICU stay (*p* value <0.0001); **B**. Survival curves based on the gender. The group of female patients had good 5 -year survival (*p*<0.05). **C.** Kaplan Meier curves for booked and un-booked patients (*p*=0.08 "just significant difference"). **D.** Survival curves associated with age of patient. The cut-point at the mean age (60.5 year) was not shows any significant (Log Rank test, *p*=0.2).



Our results demonstrate that patients with acute emergency presentation of respiratory, cardiovascular, and hepatic failure or septic shock are found to be associated with poor outcome. The study has found that outcome of the ICU patients are significantly influenced by length stay (*p*<0.0001, log-rank test), pattern of acute emergency presentation (*p*<0.0001), specific cancer diagnoses (*p*=0.02), and male gender (*p*=0.05). Patients discharged from ICU after a short length stay are significantly poorer survival compared to patients discharged from the ICU after more length stay (Table 3 and Fig. 2). Furthermore, in univariate analysis, specific

cancer diagnoses (particularly melanoma and sarcoma malignancies), older age, male gender, are associated with high risk of ICU mortality.

We observed a non-significant changes in the survival of both different registration type (p=0.08) of admission and both different years of admission (p=0.05). Patients with booked registration of ICU admissions are more likely to be discharged from ICU alive compared to those with un-booked admission. Majority of these patients are received oxygen therapy, intravenous fluids, bladder catheterization, and/or pain killer.

Apache II score are analyzed in the whole material, and in groups defined by the age, gender, histological type, pattern of presentation, date of admission, method of registration and length of stay in ICU in days and follow-up.

The average of Apache II score in the whole material is (16.5), while in varies types of cancers and different acute presentation is ranged between (12.7 and 19.8) and between (5.0 and 23.5), respectively. A statistically significant correlation between the apache II score and most clinicopathological features are observed. The strongest association is observed for age group, histological diagnosis of cancers and the different acute presentations (with p value <0.0001 among all these groups). There is also significant correlation between apache score and gender group (p=0.001). The difference in the mean apache is higher in the patient who stay in ICU of 3 days and below than those stay more than 3 days, but the difference is not statistically significant (p=0.2). The type of registration and years of admission do not have a significant relationship with the Apache score.

Discussion

The present study was carried out to evaluate the most common acute presentation of cancer patients admitted to ICU and evaluate the most common tumors. The relationship was found between each acute presentation and gender, registration, duration of admission, outcome and type of tumors.

The indicators for cancer patients' emergency admission

Some studies have showed that the respiratory and gastrointestinal symptoms were the most frequent reasons for admissions (Hjermstad et al., 2013). In current study, the most common acute presentation are respiratory symptoms followed by cardiovascular symptoms, neurological symptoms and gastrointestinal symptoms (26.9%, 23.1%, 11.1%, and 9.0% respectively).

The study has been found highly significant relation between the acute presentations and the type of cancers (p<0.0001), the outcome (p<0.0001), and the length of admission (p<0.0001), (Tables 2 and 3). In most cases, the symptoms had developed over a few days, and admitted to the medical oncology unit before the ICU. 18 patients had a more acute onset with symptoms developing within a first 12 h before admission, two patients received already died.

Distribution of registration among studied ICU patients

In current study, we have found that about 7.0% of ICU patients were diagnosed as cancer patients during an emergency admission period, which is lower than the results from Cancer Research UK report in 2012 by network of National Cancer Intelligent who concluded that about 20% of cancer patients are diagnosed through an emergency presentation (NCIN, 2012). This difference might be due to small number of un-booked patients in this study.

Acute emergency patterns and clincopathological features

Gender and age at ICU presentation: Yucel et al. (2012) noted that males and old age were correlated with incidence of ICU admission, current study has recognised a similar association between males and old age and acute emergency incidence (Table 3). The occurrence of emergency status in Libyan advance cancer patients is strongly related to the male (61.0%) and old age. The mean age was 60.5 year (range 9-98). Difference between the mean ages of men and women patients is statistically significant (p value <0.0001). This substantial difference might be due to the majority of gastrointestinal tract, breast, gynecological and thyroid cancers in Libya are seen more in young female patients (Boder et al., 2011; Abdalla et al., 2014; Sabratha Cancer Registry, 2008).

Stage: All patients in current study had advanced metastatic disease, which are the main causes of emergency admission. The advanced presentation of our

patients may be because the biological aggressiveness of these Libyan cancers or affecting the delay-time of diagnosis that could be further explaining the increase risk of advanced tumors (Ermiah et al., 2012).

Cancer types among the studied ICU patients: Our results are consistent with the results found by Yucel et al (2012) the most common primary cancer sites were lung, gastrointestinal system, hematolymphoid tissue and genitourinary system. Increase of these tumors could be explained by the aggressiveness of these cancers and the frequent requirement of palliative care appointment from oncologists. Indeed, studies from our institution and from others have consistently demonstrated that patients with hematologic malignancies have common ICU admissions and ICU deaths (Yates and Barrett, 2009).

ICU length of staying

Clearly, current study and study of Hjermstad et al. (2013) recognized that many patients required just shorter length of ICU staying, and relatively simple medical interventions such as hydration, bladder catheterization, oxygen therapy and pain killer were most frequently performed which can be given in the primary palliative healthcare sector. In the United States, and other developed countries approximately half of all hospitals provide palliative healthcare services through the acute palliative care units (APCUs), where acutely ill patients receive intensive symptom support from specialized expert team (Verdecchia et al., 2007; Earle et al., 2003; Yates and Barrett, 2009; Barbera et al., 2010; NCIN, 2012; Higginson and Evans, 2010). One study reported that systematic implementation of a palliative care integration project resulted in significantly better control of pain, and significant reduce admissions to ICU of hospitals (Dudgeon et al., 2008).

Survival analysis

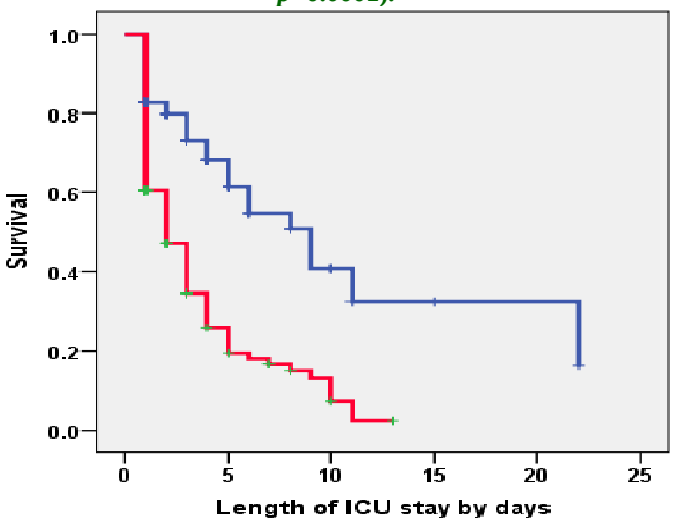
The outcome of our study, we have found that 180 cases were died (55.6%) and 144 were improved and transfer to oncology medical unit (44.4%).Our results demonstrated that patients with acute presentation of respiratory, cardiovascular, and hepatic failure or septic shock were found to be associated with poor outcome.

However, it seems that mortality rate in critical ill cancer patients admitted to our ICU is slightly higher than the results found by Hui et al. (2012), this rate is in agreement with the 58% of patients admitted because of medical complications that reported by Soares et al. (2010). The patients direct admitted from home (un-booked patients) were associated with higher mortality rate in the ICU than booked patient. This might be due to daily in diagnosis of pulmonary thromboembolism (PT), cardiac arrhythmia or myocardial infarction (MI) as a result of absent baseline ECG which very important in diagnosis PT and MI.

On other hand, the patients who transferred to ICU from the oncology medical unit had baseline ECG and prophylactic antithrombotic agents and those particularly lung cancer patients who died later within 24 h they complained of multi-organ failures rather than deaths from acute events such as thromboembolism or cardiac arrhythmia (Soares et al., 2010; Soares et al., 2007).

On other hand, the patients who died immediately after transferred from ICU to the medical unit might be due to inaccurate decision of ICU staff. However, the transfer or discharge of patients against medical advice among our population is not uncommon and could be another explanation for this failure.

Fig. 3: Kaplan Meier outcome curves for ICU patients according to mean of Apache II score (Log Rank test, *p*<0.0001).



Several studies suggest many scores to produce an applicable prediction and prognostication system for ICU patients (Moran et al., 2008; Schellongowski et al., 2004; Niskanen et al., 1991). Our results suggested that the mean value of Apache II score (16.5) is a significant cut point in Libyan material, which could separate patients into two subgroups with favourable and unfavourable prognosis (Fig. 3).

Further studies are recommended to produce a perfect prediction and prognostication system that may help ICU doctor's decision-making.

Conclusion

The acute respiratory failure, cardiovascular accident, sepsis, and bleeding were the most common causes of admission to our Intensive Care Unit. Although patients with advanced cancers may benefit from intensive supportive management of organ failures, the current study still showed poor outcomes in those patients. The high mortality rates were significantly influenced by ICU length stay, old age, male gender, histological type of cancer and pattern of acute emergency presentation. Appropriate oncology medical care such as pain management, hydration, and family doctor cooperation might be highly recommended to reduce a number of patient that need real ICU services.

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