168

The Open Nursing Journal

RESEARCH ARTICLE

Predictive Performance of two Measures of Prognostic Mortality of Cancer Patients in Intensive Care Unit in Jordan: A Comparative Single-Centre Study

Issa M. Almansour[1,*] , Mohammad K. Aldalaykeh[2] , Zyad T. Saleh[1] , Khalil M. Yousef[1] and Mohammad M. Alnaeem[1]

[1]*Department of Clinical Nursing, School of Nursing, The University of Jordan, Jordan. Amman 11942-Jordan*
[2]*TDepartment of Mental Health, 2The University of Science and Technology, Amman 11942-Jordan*

Abstract:

Background:

Information is presently insufficient about using Acute Physiology and Chronic Health Evaluation (APACHE) mortality predicting models for cancer patients in intensive care unit (ICU).

Objective:

To evaluates the performance of APACHE II and IV in predicting mortality for cancer patients in ICU.

Interventions/Methods:

This was a retrospective study including adult patients admitted to an ICU in a medical center in Jordan. Actual mortality rate was determined and compared with mortality rates predicted by APACHE II and IV models. Receiver operating characteristic (ROC) analysis was used to assess the sensitivity, specificity and predictive performance of both scores. Binary logistic regression analysis was used to determine the effect that APACHE II, APACHE IV and other sample characteristics have on predicting mortality.

Results:

251 patients (survived=80; none-survived=171) were included in the study with an actual mortality rate of 68.1%. APACHE II and APACHE IV scores demonstrated similar predicted mortality rates (43.3% *vs*. 43.0%), sensitivity (52.6% *vs*. 52.0%), and specificity (76.3%, 76.2%), respectively. The area under (AUC), the ROC curve for APACHE II score was 0.714 (95% confidence interval [CI] 0.645–0.783), and AUC for APACHE IV score was 0.665 (95% CI 0.595–0.734).

Conclusions:

As APACHE II and IV mortality models demonstrate insufficient predicting performance, there is no need to consider APACHE IV in our ICU instead of using APACHE II as it has more variables and need longer data extraction time.

Implications for Practice:

We suggest that other approaches in addition to the available models should be attempted to improve the accuracy of cancer prognosis in ICU. Further, it is also required to adjust the available models.

Keywords: Cancer, Intensive care unit, Mortality prediction, APACHE II, APACHE IV, Chronic cardiovascular and circulatory disease.

1. INTRODUCTION

Cancer continues to be one of the leading causes of death worldwide [1, 2]. In Jordan, cancer is the second leading cause of death after chronic cardiovascular and circulatory disease with an estimated 4,000 new patients diagnosed annually [3, 4]. Most new cancer patients present at advanced stages III/IV, with majority of those dying within one year of diagnosis [3, 5]. Consequently, an increasing number of cancer patients is at

* Address correspondence to this author at the Department of Clinical Nursing, School of Nursing, The University of Jordan, Jordan. Amman 11942-Jordan, Tel: +962 6 5355000; E-mail:i.almansour@ju.edu.jo,

risk of admission to intensive care unit (ICU) due to cancer-related complication or the infectious and toxic adverse effects of its treatments [6 - 8]. Despite the aggressive management provided in ICU, the mortality rate associated with cancer remains high [7, 9, 10]. Minimizing the admission of terminally ill cancer patients to ICU is considered a common practice in industrialized countries [11]. However, admitting those patients to ICUs is more common in Jordan [12 - 14]. Since ICUs in the developing countries have limited resources, an objective indicator predicting the mortality among cancer patients is needed to guide clinical decisions, avoid unnecessary procedures, and ensure optimal use of ICU resources [15 - 17].

Illness severity measures are widely used to predict mortality among the patients with wide range of health conditions in ICUs [18]. Acute Physiology and Chronic Health Evaluation (APACHE) is commonly utilized validated measure in research and clinical practices [19]. APACHE scores estimate disease severity based on the presence of several clinical conditions and physiological and laboratory parameters obtained at admission and/or during the first 24 hours after ICU admission. APACHE has been modified several times for an attempt to improve the prediction accuracy of patients' outcomes. APACHE II is the simplest validated version in predicting mortality and still utilized in ICUs worldwide as well as in Jordan. [18, 20] APACHE IV is the latest updated version that has been designed to include other significant health status parameters to predict health outcomes. Studies validating the predictive performance of APACHE II scoring system among ICU patients with cancer suggests that its predicting ability remains suboptimal [20 - 23]. A contrary result was also documented [24, 25]. APACHE IV model on the other hand was validated only in one study [24]. The study only included critically ill patients with non-haematological and non-metastatic cancer and demonstrated a good predicting ability

However, it remains unclear whether APACHE IV is superior to APACHE II in predicting mortality in the ICU among patients with different types and stages of cancer. Comparing the predictive performance of APACHE II and APACHE IV in predicting mortality will potentially help in risk stratification and utilization of proper resources for patients with cancer. The aim of this study was to compare the predictive performance of APACHE II and APACHE IV in predicting ICU mortality using data at the time of ICU admission among Jordanian patients with cancer.

2. METHODS

2.1. Study Design

This was a retrospective single-center cohort study conducted in an ICU of a hospital located in a comprehensive medical center in Jordan (King Hussein Medical Center). The center is a medical compound of five hospitals affiliated with the major Jordanian royal medical services hospitals. The center provides medical service to 38% of the Jordanian population and is considered one of the most important medical centers in Middle East and the whole world. The study hospital has thirty six beds ;adult ICU provide a Western-style critical

medicine for critically ill patients with different medical illnesses including cancer.

This study is a part of a project aimed at examining demographics, mortality, cause of death and healthcare utilization for those who died in the studied ICU over a 3-year period (2014, 2015, and 2016). Data from previous years were difficult to retrieve due to poor record keeping system. APACHE II and APACHE IV scores were calculated using an online calculator. The clinical conditions and the physiological and laboratory parameters required to compute the scores of both models were retrieved from medical record. The scores for APACHE II and APACHE IV models were calculated based on the first 24 hrs of ICU admission. ICU mortality was assessed through electronic medical records. Data were collected by a team of researchers between January 2017 and January 2018. The researchers retrieved relevant data for a small subset of records and calculated APACHE IV scores to make sure the data are collected in a uniform way by all reviewers.

2.2. Ethical Considerations

The study was reviewed by the School of Nursing Research Ethics Committee, University of Jordan (Reference: 26-4-2016 SON) and by the Ethics Committees of the study medical center (Reference: TF 3/1/Ethics/13686). The ethics boards determined that the requirement to obtain informed consent from patients was waived due to the study's retrospective nature

2.3. Statistical Analysis

Data were analysed using Statistical Package for Social Science software 22 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were used to describe the study sample and to summarize APACHE II and IV scores. Predicted mortality rates were determined using APACHE II and APACHE IV models and compared with actual mortality rate. Receiver operating characteristic (ROC) analysis was used to assess the sensitivity, specificity and predictive performance for mortality by both models. Lastly, two multiple binary logistic regression models were used to compare the predictive ability of APACHE II and APACHE IV for mortality. In both models, the outcome (dependent) variable was mortality whereas, APACHE II and APACHE IV were the independent variables. Both models were adjusted for the following covariates gender, type of cancer, and sepsis. An alpha level of less than 0.05 was used to determine statistical significance. The 95% confidence interval was also used to test for significance in this study. The 95% confidence interval offers evidence regarding the range of the actual data as well as magnitude of the relationship between the independent and the dependent variable. Therefore, using the 95% confidence interval allows for assessing the clinical significance in addition to the statistical significance. It also offers information about the nature of the relationship between the variables, *i.e*. negative or positive.

3. RESULTS

Two hundred and fifty-one patients (survived=80; none-

survived=171) were included in the study with an average age of 54.9±15.4 years (survived=53.4±16.8; none-survived= 55.7±14.7). The percentages of male and female in the sample were 56.3% and 43.7%, respectively. Compared to survivors, the proportion of patients with sepsis was higher among non-survived patients (*p*=.003). Patients who survived their ICU stay had significantly lower APACHE II and APACHE IV score (19.3±7.5 and 76.5±22.3, respectively) compared to those who did not survive (25.4±7.9 and 90.8±22.4, respectively), *p*<.001. The predicted mortality of APACHE II and APACHE IV were significantly lower among survivors (30.5±22.1% and 37.3±21.2%, respectively) compared to non-survivors (51.0±23.3% and 59.1±22.9%, respectively), *p*<.001. The characteristics of the study sample and comparison between survival and non-survival patients are provided in Table **1**.

Figs. (**1** and **2**) show the actual mortality rate for each APACHE II and IV score category, respectively. For instance, there was only 1 patient in the category of APCHE II score of 0-4 and no survivors in this category which resulted in 100% mortality rate, while the category of 5-9 had no non-survivors which resulted in 0% mortality rate. The figure of APACHE II model shows that the higher the APCHE II score, the greater the mortality rate. For APACHE IV model, there was a general increase in mortality rate with increasing model scores.

In this study, the actual mortality rate in our sample was 68.1%. APACHE II and APACHE IV models demonstrated similar predicted mortality rates (43.3% *vs*. 43%), sensitivity (52.6% *vs*. 52%), and specificity (76.3%, 76.2%), respectively. Table **2** shows APACHE II and APACHE IV predicted outcome *versus* observed outcome cross tabulation. The area under the curve (AUC) in APACHE II score (71.4%) was slightly higher than the AUC for APACHE IV score (66.5%) (Table **3**). Multivariate binary logistic regression revealed that APACHE II score (OR 1.11, 95% CI 1.073-1.17, *p* = .03) and APACHE IV score (OR 1.03, 95%CI 1.01-1.05, *p* = .01) were independently associated with higher mortality in cancer patients who needed ICU support (Table **4**).

4. DISCUSSION

This retrospective cohort study of 251 cancer patients evaluated the performance of APACHE II and APACHE IV scores in predicting mortality in cancer patients. This is one of the few studies on assessing the performance of these models among critically ill cancer patients; the first in Middle East. The results revealed that higher scores of both APACHE II and IV at ICU admission are associated with higher mortality rate. However, the predictive and performance of both scores was insufficient for predicting ICU mortality. Both prognostic models had similar predictive sensitivity and specificity and provided similar ability prediction for mortality in this sample. Furthermore, the AUC of the ROC curve for both models demonstrate a comparable moderate predicting ability. Even though there a statistical significance in the regression models, OR were very small suggesting weak clinical significance for both APACHE II and APACHE IV in predicting mortality in this sample.

Our findings regarding APACHE II score corroborates other findings in the literature [21 - 24]. Evidence suggests that while APACHE II score is a significant predictor for ICU mortality, it can be used to prognosticate about cancer patients in ICU and remains suboptimal predictor of mortality in patients with cancer. To a lesser extent, other studies reported a good predictive performance for APACHE II model [25, 26].
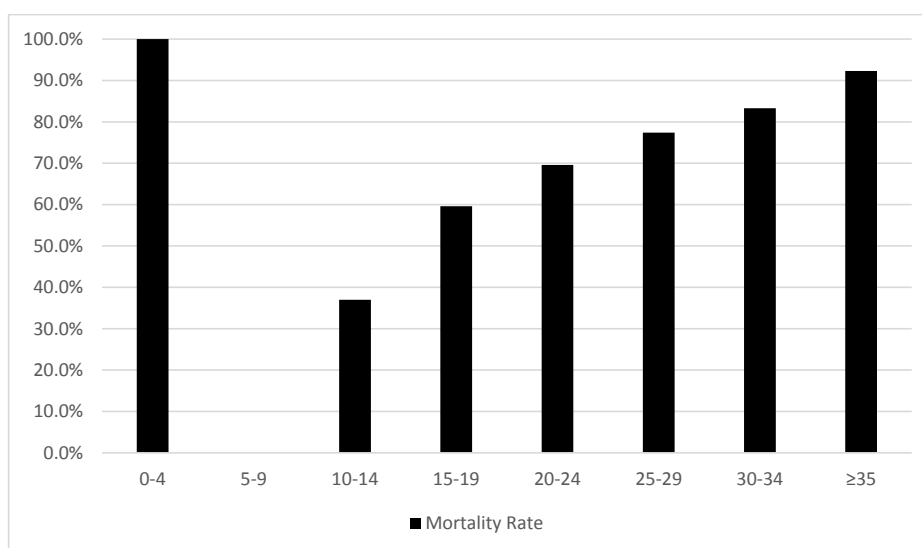

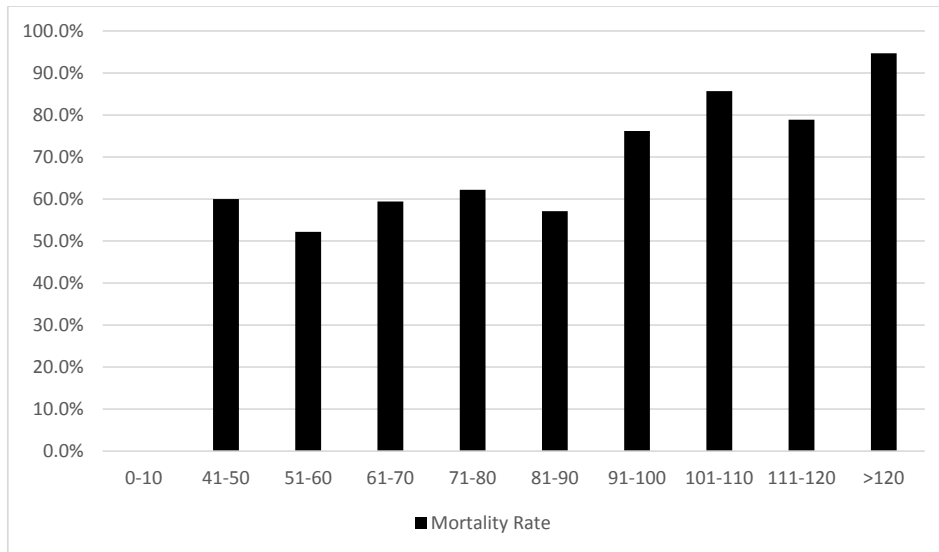**Fig. (1).** Mortality Rate for Each APACHE II Score Category.

Fig. (2). Mortality Rate for Each APACHE VI Score Category.

Table 1. The Demographic Characteristics of Survived and Non-survived Samples

Variable	Survived (N=80)	None-survived (N=171)	*P*
Average Age ± SD (Range)	53.4±16.9 (21.82)	55.7±14.7 (20-91)	.096[a]
Gender N (%)	-	-	-
Male	49 (61.3)	92(53.8)	.278[b]
Female	31 (38.8)	79(46.2)	-
Type of cancer N (%)	-	-	-
Hematological	26 (32.5	67 (39%)	.329[b]
Solid	54 (67.5)	104 (61%)	-
Sepsis N (%)	-	-	-
Yes	36 (37.5)	111 (65%)	.003[b]
No	44 (62.5)	60 (35%)	-
APACHE II Score (Mean ± SD)	19.33±7.51	25.43±7.89	<.001[a]
APACHE IV Score (Mean ± SD)	76.50±22.30	90.79±22.35	<.001[a]
APACHE II Predicted Mortality (Mean ± SD)	30.5±22.1%	51.0±23.3%	<.001[a]
APACHE IV Predicted Mortality (Mean ± SD)	37.3±21.2%	59.1±22.9%	<.001[a]

[a] T-test, [b] Chi-Sequare

Table 2. APACHEII and APACHE IV Predicted Outcome vs. Observed Outcome Cross Tabulation

		Outcome		Total
		Non-survival (N)	Survival (N)	
APACHE II Prediction	Non-survival	90	19	109
	Survival	81	61	142
APACHE IV Prediction	Non-survival	89	19	108
	Survival	82	61	143
Observed		171	80	251

Observed mortality rate 68.1
APACHE II predicted mortality rate 43.4%
APACHE IV predicted mortality rate 43%
APACHE II Sensitivity=52.6%, Specificity=76.3%, Cut off value=24.5
APACHE IV Sensitivity=52%, Specificity=76.2%, Cut off value=90.5

Table 3. The AUC of APACHE II and APACHE IV Scores

-	Area	Std. error	Sig.	95% CI	
				Lower bound	Upper bound
APACHEII	0.714	0.035	0.000	0.645	0.783
APACHEIV	0.665	0.035	0.000	0.595	0.734

Table 4. Summary of Multiple Binary Logistic Regression Analysis (Survival Status as a Dependent Variable)

Variable	OR	*P*	95%CI for OR	
			Lower	Upper
APACHE II	1.119	<.001	1.073	1.167
Gender	1.412	.258	.777	2.566
Sepsis	4.064	.001	1.742	9.484
Type of cancer	1.846	1.846	.776	4.391
APACHE IV	1.031	<.001	1.017	1.046
Gender	1.466	.198	.819	2.626
Sepsis	3.763	.002	1.636	8.659
Type of cancer	2.312	.059	.969	5.518

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error

There is a paucity of information in the literature about APACHE IV score in critically ill cancer patients. In a recent study in China [25], the predictive performance of APACHE II and APACHE IV scores was evaluated in 981 cancer patients admitted to ICU and both scores demonstrated good discrimination and calibration ability. However, this study did not include patients with haematological cancer and the majority of patients had non-metastatic tumors. In our study, more than one third of patients had haematological cancer and the majority had stage III and IV tumor. These differences may explain the discrepancy in findings and also suggest the need for modified version of APACHE scores specific for patients with cancer. To our knowledge, this is the only study that validated APACHE IV model in critically ill cancer patients. Validating this score among Jordanian patients with specific cancer characteristics might yield a different result.

In this study, sepsis was found to have a significantly unfavourable association with cancer mortality in ICU with an OR of 4.1 and 3.8 in APACHE II and APACHE IV models, respectively. Other prognostic variables in addition to sepsis were reported in the literature including poor patient performance status, stage or nature of malignancy, provision of intensive treatments (ventilator support, vasoactive medication, and renal-replacement therapy), and the time of last chemotherapy [21, 23]. Adjusting for these variables may improve the predictive performance of APACHE scores. For example, Martos-Benítez *et al*. adjusted APACHE II prediction model for clinical stage of cancer, use of mechanical ventilator, and reason for admission (malignancy and non-malignancy) [21] The adapted model was validated with 522 patients admitted to ICU with solid cancer and demonstrated a better discrimination and calibration compared to the original one.

There are several limitations for our study. For example this was retrospective study which restricted the ability to collect further data about the sample. Also, only a single medical center was utilized. Lastly, we did not collect data about variables that could have been important in our prediction models such as the stage of cancer and the length of ICU stay.

CONCLUSION

Predicting mortality in ICU cancer patients is difficult due to variability in stages, performance status, and other cancer specific criteria. Even though the predictive ability of APACHE II and APACHE IV models was established, their performances were insufficient. There is a need to further explore and consider other typical prognostic variables related to cancer patients. A prospective study that may adjust for cancer specific variables is recommended to improve the predictability of APACHE scores.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was reviewed by the School of Nursing Research Ethics Committee, University of Jordan (Reference: 26-4-2016 SON) and by the Ethics Committees of the study medical center (Reference: TF 3/1/Ethics/13686).

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

The data that support the findings of this study are available from the corresponding author. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the corresponding author with the permission of the ethical committee of King Hussein Medical Center.

FUNDING

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGMENTS

REFERENCES

[1]   WHO. World Health Organization (WHO) . Cancer. Geneva, Switzerland: WHO, Title. Available at: http://www.who.int/mediacentre/factsheets/ fs297/en/ Published 2015.

[2]   Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(6): 394-424.
[http://dx.doi.org/10.3322/caac.21492] [PMID: 30207593]

[3]   MOH. Jordan Cancer Registry. Available at: https://moh.gov.jo/Echobusv3.0/System Assets/fbd82c46-6851-40d5-ae9f-651dfc9515ec.pdf pdf. Published 2015. Accessed December 11, 2019

[4]   Nazer LH, Tuffaha H. Health care and pharmacy practice in Jordan. The Canadian journal of hospital pharmacy
[http://dx.doi.org/10.4212/cjhp.v70i2.1649]

[5]   Stjernswärd J, Ferris FD, Khleif SN, *et al.* Jordan palliative care initiative: a WHO Demonstration Project. J Pain Symptom Manage 2007; 33(5): 628-33.
[http://dx.doi.org/10.1016/j.jpainsymman.2007.02.032] [PMID: 17482059]

[6]   Bos MMEM, Verburg IWM, Dumaij I, *et al.* Intensive care admission of cancer patients: a comparative analysis. Cancer Med 2015; 4(7): 966-76.
[http://dx.doi.org/10.1002/cam4.430] [PMID: 25891471]

[7]   Sauer CM, Dong J, Celi LA, Ramazzotti D. Improved Survival of Cancer Patients Admitted to the Intensive Care Unit between 2002 and 2011 at a U.S. Teaching Hospital. Cancer Res Treat 2019; 51(3): 973-81.
[http://dx.doi.org/10.4143/crt.2018.360] [PMID: 30309220]

[8]   Darawad MW, Al-Hussami M, Saleh AM, Al-Sutari M, Mustafa WM. Predictors of ICU patients' pain management satisfaction: A descriptive cross-sectional survey. Aust Crit Care 2015; 28(3): 129-33.
[http://dx.doi.org/10.1016/j.aucc.2014.07.003] [PMID: 25444456]

[9]   Aygencel G, Turkoglu M, Turkoz Sucak G, Benekli M. Prognostic factors in critically ill cancer patients admitted to the intensive care unit. J Crit Care 2014; 29(4): 618-26.
[http://dx.doi.org/10.1016/j.jcrc.2014.01.014] [PMID: 24612762]

[10]   Almansour IM, Ahmad MM, Alnaeem MM. Characteristics, Mortality Rates, and Treatments Received in Last Few Days of Life for Patients Dying in Intensive Care Units: A Multicenter Study. Am J Hosp Palliat Med 2020; p. 1049909120902976.

[11]   Schellongowski P, Sperr WR, Wohlfarth P, *et al.* Critically ill patients

with cancer: chances and limitations of intensive care medicine-a narrative review. ESMO Open 2016; 1(5)e000018
[http://dx.doi.org/10.1136/esmoopen-2015-000018] [PMID: 27843637]

[12]   Almansour. Transitioning towards end-of-life care in Jordanian critical care units: health care professionals' perspectives 2015.

[13]   Hawari FI, Nazer LH, Addassi A, Rimawi D, Jamal K. Predictors of ICU admission in patients with cancer and the related characteristics and outcomes: a 5-year registr-based study. Crit Care Med 2016; 44(3): 548-53.
[http://dx.doi.org/10.1097/CCM.0000000000001429] [PMID: 26562345]

[14]   Almansour I, Seymour JE, Aubeeluck A. Staff perception of obstacles and facilitators when providing end of life care in critical care units of two teaching hospitals: A survey design. Intensive Crit Care Nurs 2019; 53: 8-14.
[http://dx.doi.org/10.1016/j.iccn.2019.04.003] [PMID: 31023516]

[15]   Huaringa AJ, Francis WH. Outcome of invasive mechanical ventilation in cancer patients: Intubate or not to intubate a patient with cancer. J Crit Care 2019; 50: 87-91.
[http://dx.doi.org/10.1016/j.jcrc.2018.11.014] [PMID: 30502688]

[16]   1de Jonge E, van Raalte DH, Diamant M, *et al.* Patients with cancer on the ICU: Time for optimism. Neth J Med 2014; 72: 60-1.

[17]   Hui D. Prognostication of survival in patients with advanced cancer: predicting the unpredictable? Cancer Contr 2015; 22(4): 489-97.
[http://dx.doi.org/10.1177/107327481502200415] [PMID: 26678976]

[18]   Rapsang AG, Shyam DC. Scoring systems in the intensive care unit: a compendium. Indian J Crit care Med peer-reviewed, Off Publ Indian Soc. Crit Care Med 2014; 18(4): 220.

[19]   Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med 1981; 9(8): 591-7.
[http://dx.doi.org/10.1097/00003246-198108000-00008] [PMID: 7261642]

[20]   John S. Intensive Care in Oncology: Admission and Outcomes in Adult Patients with Cancer 2016.

[21]   Martos-Ben'itez FD, Cordero-Escobar I, Soto-Garc'ia A, Betancourt-Plaza I, González-Mart'inez I. APACHE II score for critically ill patients with a solid tumor: A reclassification study.Rev Española Anestesiol y Reanim (English Ed). 2018; 65: pp. (8)447-55.

[22]   Geerse DA, Span LFR, Pinto-Sietsma SJ, van Mook WNKA. Prognosis of patients with haematological malignancies admitted to the intensive care unit: Sequential Organ Failure Assessment (SOFA) trend is a powerful predictor of mortality. Eur J Intern Med 2011; 22(1): 57-61.
[http://dx.doi.org/10.1016/j.ejim.2010.11.003] [PMID: 21238895]

[23]   Kopterides P, Liberopoulos P, Ilias I, *et al.* General prognostic scores in outcome prediction for cancer patients admitted to the intensive care unit. Am J Crit Care 2011; 20(1): 56-66.
[http://dx.doi.org/10.4037/ajcc2011763] [PMID: 21196571]

[24]   Karaoren G, Akbas S, Serin SO, *et al.* Hospice Units as a requirement for terminal stage patients in need of intensive care in Turkey. Int J Clin Exp Med 2016; 9(7): 14907-12.

[25]   Xing X, Gao Y, Wang H, *et al.* Performance of three prognostic models in patients with cancer in need of intensive care in a medical center in China. PLoS One 2015; 10(6)e0131329
[http://dx.doi.org/10.1371/journal.pone.0131329] [PMID: 26110534]

[26]   Martos-Ben'itez FD, Larrondo-Muguercia H, León-Pérez D, Rivero-López JC, Orama-Requejo V. others. Performance of Three Prognostic Models in Critically Ill Patients with Cancer: A Prospective Study. Int J Cancer Clin Res 2019; 6: 120.