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How can we detect delirium easier among oncologic patients in the Emergency Department?

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AİM: The study was planned to assess delirium for the oncologic patients admitted to ED with the complaint of altered level of consciousness, based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnostic criteria, research for influencing etiologic factors and comparison of the brief Confusion Rating Method (bCAM), Mini Mental State Examination (MMSE) and New Delirium Rating Scale (NDRS), which are considered as delirium screening tests.
Methods: The Richmond Agitation-Sedation Scales (RASS) calculated for all patients before applying bCAM. The patients with the RASS score between -3 and +4 had been evaluated with bCAM. Delirium was diagnosed when the third or fourth characteristic was positive as well as the first two. The MMSE and NDRS scores of all patients and the duration of three tests were calculated.
Results: The MMSE and NDRS scores were 13,46±3,78 (7-20) and 21,42±3,28 (11-26) in the patients who were in delirium, respectively. Harmony between bCAM and MMSE are also statistically significant (Eta=0,70). Application period of bCAM was the shortest as 46,92±6,16 (30-60) sec.
Conclusion: bCAM was applied in the shortest period of time. This result is very useful for the EDs which are racing against time in the world.

Keywords: delirium, cancer patient, bCAM, NDRS, emergency department
Short Title in English: Detecting delirium among oncologic patients

INTRODUCTION

Among cancer patients' cognitive problems are the most frequently reported symptoms during treatment, especially related to chemotherapy (1) and with a prevalence of delirium occurring in as many as 88% of patients with advanced cancer (2). As delirium impairs recognition of physical symptoms, it complicates achieving optimal symptom management, especially pain control in the emergency department (ED). Furthermore, delirium in patients with cancer is associated with significantly longer hospital stays, greater and longer functional decline, shorter life expectancy and a greater risk of death during acute treatment (3).

A diagnosis in the ED could help to optimize therapeutic approaches and improve clinical outcomes and potentially lower health care costs. Despite its importance of early recognition and treatment, the frequency of delirium among patients with cancer presenting to the emergency department is still unknown and often missed or misdiagnosed as worsening pain, depression, or anxiety (4).

Due to dynamic environment prolonged assessments for delirium are not appropriate in the ED settings and brief and sensitive tools are needed. As a tertiary care, academic ED,

cancer patients visiting our emergency department have higher rates and longer lengths of stay in ED.

The Mini Mental State Examination, the brief Confusion Assessment Method (bCAM), and the New Delirium Rating Scale (NDRS) are used for quantitative measurement of cognitive status in adults.

Therefore, in this study we intend to assess delirium for the patients admitted to ED with the complaint of altered level of consciousness with a known malignancy, based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnostic criteria, research for influencing etiologic factors and comparison of the bCAM, MMSE and NDRS, which are considered as delirium screening tests.

MATERIALS and METHODS

This was a prospective observational study. Local institutional ethics committee approval was obtained from XXXXX University in October 2015 (GO 15/655-23). Written informed consent was obtained from all participants.

This study was set up between November 15, 2015 and May 31, 2016. The patients over 18 years of age who admitted to ED with the complaint of altered level of consciousness with a known malignancy were included in the study. Patients who left the ED without permission, those who refused, or were unable to participate were excluded from the study.

For each patient; age, gender, duration of consciousness blurring, existing malignancy, whether the patient had a similar complaint earlier, if so how long ago it took place, previous diagnosis, consultations, outcome, Glasgow Coma Scale (GCS) were recorded.

If the patients had the complaint of altered level of consciousness previously, this situation has been separated to 0-1 month, 1-6 months or >6 months' sections. The diagnoses have been grouped as; neurological, infectious, cardiopulmonary diseases, metabolic or electrolyte disorder, trauma, drug induced, psychiatric and other diseases. The outcome of the patients stated as; discharged/exitus in ED, discharged/exitus in the ward, discharged/exitus in intensive care unit (ICU).

RASS calculated for all of the patients before applying the bCAM. Delirium evaluation could not be made when the RASS score was -4 or -5. In pursuance of reference diagnosis, we determined according to the fourth version of the Diagnostic and Statistical Manual of Mental

Disorders (DSM-IV). The patients with the RASS score between -3 and +4 were evaluated with the bCAM, MMSE and NDRS. The scores and the duration of each tests were calculated.

bCAM has 4 features: altered mental status, or fluctuating course, inattention, altered level of consciousness and disorganized thinking (Figure 1) (5). Delirium was diagnosed due to the bCAM when both features 1 and 2 were present and either features 3 or 4 was present. MMSE can be implemented in a short time and its validity has been proven. It assesses orientation, recall, retention, and language ability. The NRDS which was developed by Ok et al. for intensive care settings, evaluates the cardinal features of delirium, such as acute or fluctuating onset, inattention, disorganized thinking and altered level of consciousness. It is a 10-item, observer-rated scale based both on DSM-IV and on symptoms drawn from previous clinical research (Figure 2) (6).

Study protocol is given in the Figure 3.

SPSS for Windows version 20 program was used for the statistical analysis of the findings obtained in the study. Numerical variables were shown with average ± standard deviation or median (minimum-maximum); attribute variables were shown in numbers and percentages. The difference between the groups in terms of attribute variables was investigated by chi-square test. In case of occurrence whether there is a difference or not in numerical variables between the two groups depending on the parametric test assumptions evaluated according to t-test in independent groups, and in the other case according to Mann Whitney U test. The significance level was determined as $p < 0.05$.

RESULTS

Totally 195 patients were included; 112 (57,4%) were male and 83 (42,6%) were female. The average age of these patients were 69 (25-92).

The present malignancies of the patients are shown in Figure 4. The most common malignant disease was lung neoplasm in 60 patients (30,8%). The most common diagnosis was pneumonia in 85 patients (43.6%).

According to the DSM-IV diagnostic criteria and results of bCAM, MMSE and NDRS tests, delirium was diagnosed in 26 of 195 patients (13,3%), no delirium was detected in 117 patients (60%), and no test could be made to 52 patients (26,7%) with RASS -4 or -5.

No statistically significant difference was found according to gender as 13 (%50) of the 26 patients with delirium were female and 13 (%50) of them were male (p=0,353). No statistically significant difference was found according to age as the average age of the 26 patients with delirium was 68,04±12,49, and 117 patients without delirium were 66,53±11,38 (p=0,548) (Table 1).

We found that the presence of accompanying illness increased the risk of delirium and 100% of patients with delirium were found to have an accompanying disease rather than a malignancy (Table 2). Among 26 patients with delirium 9 patients (34,5%) were accomponied by acute infection (pneumonia, urinary tract infection and typhlitis), 7 (26,9%) hepatic encephalopathy , 5 (19,2%) new diagnosis of intracranial mass and 5 (19,2%) hyponatremia diagnosis.

The mean of MMSE and NDRS scores of 26 patients with delirium was 13,46±3,78 (7-20), 21,42±3,28 (11-26) respectively; while 117 patients without delirium had a mean of MMSE scores 22,43±3,49 (6-27), and a mean of NDRS scores 8,53±0,74 (6-10). Statistically, strong positive correlation of total scores between the tests was found between bCAM and NDRS (Eta=0,95). Correlation between bCAM and MMSE was also statistically significant (Eta=0,70). Although less than the other two, correlation between MMSE and NDRS was also statistically significant (Eta=0,44). bCAM was performed in the shortest time of period among the other test, with an application period of was measured as 46,92±6,16 (30-60) seconds.Whereas the mean of application period of MMSE and NDRSA was measured as 256,89±24,31 (200-320) and 273,79±25,48 (230-360) seconds respectively (Table 3).

DISCUSSION

In a study by *Sharma et al.*; they expressed that the incidence of delirium was reported in a wide range from 11% to 87% in studies, such as the type of patient population, the type of study, and the use of various diagnostic scales (7). In our study, delirium incidence was found to be 13,3%. This result is consistent with many studies.

In our study, delirium screening tests were applied immediately after the ED admission. In a study by *Ely et al.*; it has been reported that the delirium starts on average between the second and the third day after having settled in the intensive care unit and lasts for an average of 3-4 days although it can last up to 60 days (8). In our study, patients were assessed for delirium once on all tests within the same day. This probably reduced our rate of delirium in our ED.

In a study of *Ely et al.* in which they were investigating sociodemographic characteristics of delirium; they expressed that aging is one of the factors that increase the tendency to delirium (9). In a recent study conducted in an emergency department, *Brich et al.* found that female sex was slightly higher as 53.7% (10). There was no statistically significant difference according to sex and mean age in our study. However, as the average age of the delirium group was higher, it is in line with other works done before.

In our study, 20 (77%) of patients with delirium were in terminal period of cancer. In a study held in an acute paliative care unit, delirium occurance rate in patients with advanced cancer found to be 42-45% on admission and for first onset after admission. *Lawlor* reported that delirium prevalance in ptients with cancer in the ED settings was 9% (11). Uchida et al. reported 43% insidence of delirium in advanced cance patients and 75% of the patients received a terminal prognosis (12).

In our study the most common subgroup was lung cancer similar to the *Uchida et al.* study in which lung cancer (74%) was the most common one also (12).

Sharma et al. expressed that smoking, presence of acidosis, higher APACHE-II scores and use of sedative medications were found to more frequently seen in the incidence delirium group comparing non delirius group (7). *Breitbart et al.* stated that multiple etiologies (67.3%) were more common than single etiologies as the cause of delirium among hospitalized cancer patients and in their study the most common etiologies for delirium included opioid analgesics (58.4%), corticosteroids (27.7%), systemic infection (38.6%), hypoxia (25.7%) (13). In our study we found that the presence of an accompanying illness increased the risk of delirium and all of the patients with delirium were found to have accompanying disease.

Many scales were developed for the evaluation of delirium. However, there are few current scales developed, especially for intensive care and emergency patients (9). In our study, the bCAM, MMSE and NDRS were studied on cancer patients who came to our ED with altered level of consciousness complaints.

The "Confirmation Assessment Method for the Intensive Care Unit (CAM-ICU)" was developed by *Ely et al.* for use in intensive care units to detect delirium in ICU patients who cannot normally communicate due to mechanical ventilation. In this first study where they defined CAM-ICU, 38 patients in ICU were evaluated daily with CAM-ICU by 2 nurses and 1 ICU specialist and compared to DSM-IV criteria which is accepted as a reference test. Delirium was detected in 33 of the 38 patients (87%) in ICU, and it was concluded that CAM-ICU might be a

useful tool for delirium detection when used by nurses and doctors in this difficult patient population (14). In another study, *McNicoll et al.* have compared "Confirmation Assessment Method (CAM)" and CAM-ICU. Twenty-two patients aged 65 years or older who were admitted to ICU were included in the study. Two trained clinicians interviewed each patient for 10 minutes and evaluated the patients according to four key CAM criteria; acuteness, inattention, disorganized thinking, and altered level of consciousness. One researcher used CAM method with "Mini Mental State Examination", while the other researcher used CAM-ICU. The delirium rate was 68% according to CAM, and 50% according to CAM-ICU. When two methods were compared, compliance was 82%. The differences in conclusions were accepted to be because of the fact that CAM was a more detailed cognitive test. Because of the easy application method and short-term implementation of CAM, it was concluded to be applied to ICU patients and can be used to detect latent delirium cases in intensive care patients who are able to speak and non-intubated (15).

In our study, the correspondence between bCAM and MMSE was statistically significant. This result is consistent with other studies and shows that the MMSE score is lower in patients with delirium.

Ok et al. developed NDRS as a result of the study in the ICU in Turkey in 2010. Delirium was diagnosed in 3 patients (10%) among 30 patients who were treated in the ICU for longer than 24 hours without endotracheal intubation. They admitted the cut off value for delirium diagnosis as 11 (6). In our study, the correspondence between bCAM and NDRS was statistically significant; the mean NDRS score in the patients with delirium was higher than the patients without delirium. This result is consistent with other studies and shows that the NDRS score is higher in patients with delirium.

Baten et al. (16) applied bCAM in the emergency settings during the daily work routine by emergency physicians rather than a neurologist/psychiatrist and found that bCAM took a median time of 3 minutes to perform, which is longer than our study as well as the literature and they speculated that duration of the test will be shorter when bCAM is routinely performed. When we compare the duration of the tests made in emergency service, the bCAM was shorter than MMSE and NDRS.

Although cancer patients were admitted to our ED more than surgical or medical emergencies apart from oncologic emergencies the number of the patients included in the study was fewer than expected. This was the limitation of this study.

CONCLUSION

bCAM is easier to apply to detect delirium in ED and it is more suitable for the ED patients because of its short application period. This result is very valuable to us as the EDs are units racing against time in our country and in the world.

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Table 1. Distribution of patients with and without delirium according to gender, age, and diagnosis

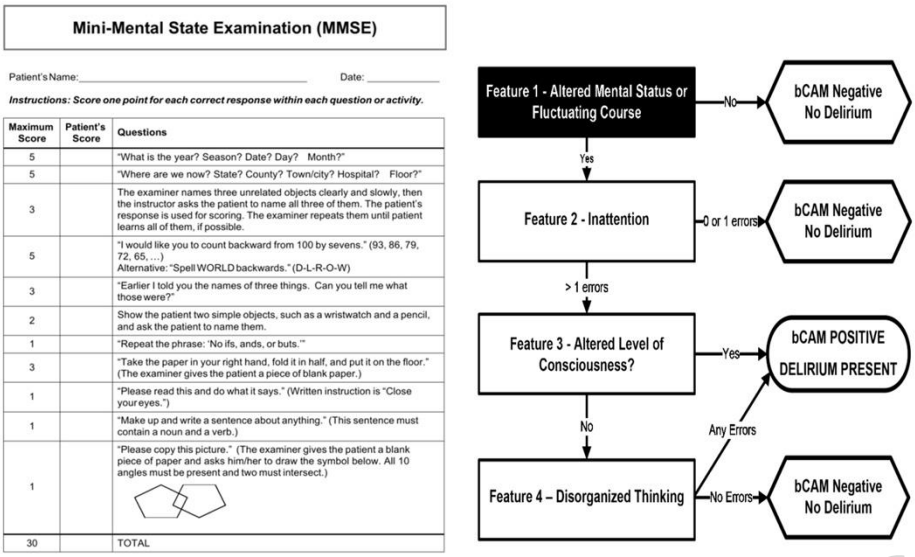
	With Delirium N=26	Without Delirium N=117	Total N=143
Gender (Female)	13 (50%)	44 (37,6%)	57 (39,8%)
(Male)	13 (50%)	73 (62,4%)	86 (60,2%)
Age (Mean±Sd)	68,04 ± 12,49	66,53 ±11,38	
Diagnosis			
Newly Diagnosed İntracranial Mass	5 (19,2%)	4 (3,4%)	9 (6,3%)
Pneumonia	5 (19,2%)	58 (49,6%)	63 (44,1%)
Urinary Tract İnfections	3 (11,5%)	13 (11,1%)	16 (11,2%)
Hyponatremia	5 (19,2%)	13 (11,1%)	18 (12,6%)
Ischemic Cerebrovascular Event	-	4 (3,4%)	4 (2,8%)
Generalized Seizure	-	5 (4,3%)	5 (3, %5)
Hepatic Encephalopathy	7 (26,9%)	-	7 (4,9%)
Carbon Dioxide Retention	-	3 (2,6%)	3 (2,1%)
Hypoglycemia	-	1 (0,9%)	1 (0,7%)
Gastrointestinal Bleeding	-	8 (%6,8)	8 (5,6%)
Cardiac Tamponade	-	2 (1,7%)	2 (1,4%)
Diabetic Ketoacidosis	-	2 (1,7%)	2 (1,4%)
Typhlitis	1 (3,8%)	4 (3,4%)	5 (3,5%)

SD: standard deviation

Table 2. MMT/NDRS scores and application period for the patients with and without delirium according to bCAM

	With Delirium	Without Delirium	Total
Delirium acoording to bCAM (n)	26	117	143
Scores			
MMT	13,46 ± 3,78	22,43 ± 3,49	20,80 ± 4,95
NDRS	21,42 ± 3,28	8,53 ± 0,74	10,87 ± 5,22
Application period [seconds±SD (min-max)]			
bCAM	46,92 ± 6,16 (30-60)		
MMT	256,89 ± 24,31 (200-320)		
NDRS	273,79 ± 25,48 (230-360)		

bCAM: Brief confusion assesment method,MMT: Mini mental test, NDRS: New Delirium, Rating Scale SD:Standard deviation,



Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)
30		TOTAL

Figure 1. The Mini Mental State Examination (MMSE) and the brief the brief Confusion Assessment Method (bCAM)

New Delirium Rating Scale (NDRS)
1) Psychomotor activity
0. Normal
1. Mild increase (agitation or restlessness) or decrease (mild retardation) in acitivity
2. Moderate increase (intending to leave the ward, grasping the tubes, groping the bed) or decrease (performing activity on command) in activity
3. Excessive increase (exitation deserving fixation) or decrease (not even performing activity on command) in activity
2) Orientation
0. Normal
1. Disorientation for time, or place, or person
2. Disorientation for time and place, or time and person, or place and person
3. Disorientation for time, and place, and person (rate no answer due to confusion here)
3) Attention
0. Normal
1. Difficulty in concentration (maintaining his/her attention by himself/herself)
2. Moderate disturbance in attention, distractibility (maintaining his/her attention on command)
3. Total disturbance in attention (not even maintaining his/her attention on command)
4) Memmory
0. Normal
1. Disturbance in immediate or recent memory
2. Disturbance in immedite and rrecent memory
3. Disturbance in immediate or recent memory (rate no answer due to confusion)
5) Perception
0. Normal
1. Vivid dreams and/or nightmares
2. Transient illusions and/or hallucinations
3. Definite illusions and/or hallucinations (hallucinatory experience)
6) Thinking
0. Normal
1. Partially disrupted thinking
2. Totally disrupted thinking
3. Incoherence
7) Thought content
0. Normal
1. Overvalued thought (does not act consistently and knows that is false)
2. Drafts of delusion (sometimes acts consistently and can inquire that it is false)
3. Delusion (acts consistently and cannot inquire that is false) or delusional experience
8) Sleep-wake cycle
0. Normal
1. Marked drowsiness daytime while being awake most of the night
2. Sleeping daytime while being awake all of the night
3. Almost not sleeping or always sleeping during both the day and the night
9) Diurnal variation
0. No fluctuation
1. Occurance of symptoms during the night while normal during the day
2. Occurance of symptoms continuously during the night and interruptedly during the day
3. Occurance of symptoms both during the day and the night fluctuatingly
10) Lability of mood
0. No fluctuation
1. Alternation or change in mood over the course of hours
2. Alternation or change in mood over the course of minutes (mood changes which are inappropiate to situation, including fear, anger or tearfulness)
3. Severse disinhibation of emotions (temper outbursts, uncontrolled laughter or crying)

Figure 2. The New Delirium Rating Score (NDRS)

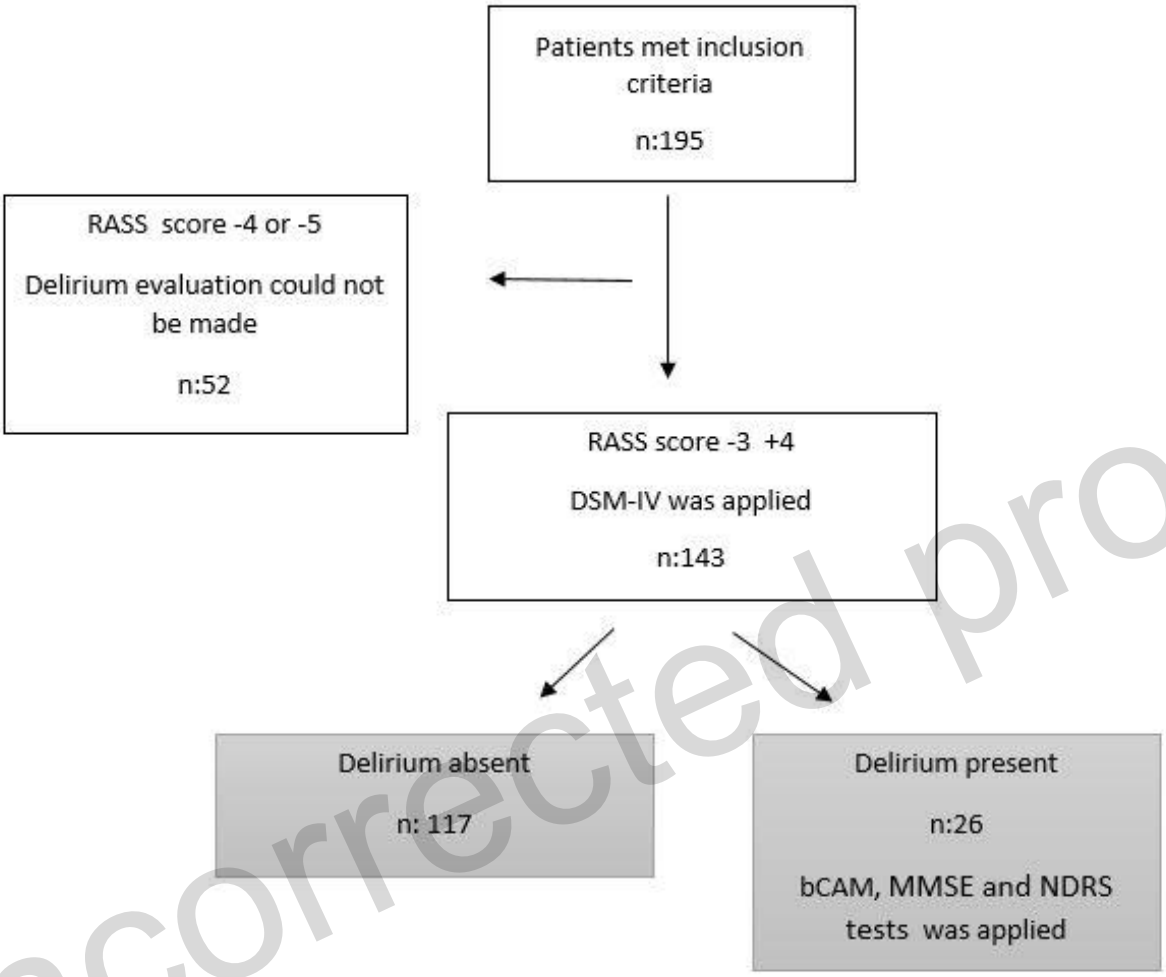


Figure 3. Study protocol

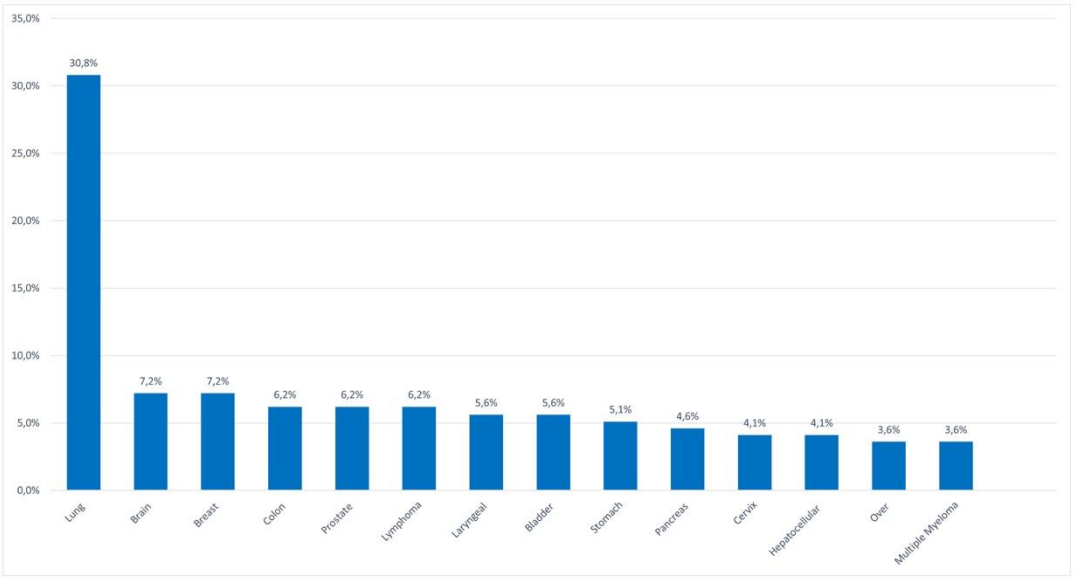


Figure 4. Distribution of the patients according to existing malignancies

ABBREVIATIONS

bCAM: Brief Confusion Assessment Method

CAM: Confirmation Assessment Method

CAM-ICU: Confirmation Assessment Method for the Intensive Care Unit

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders- IV

ED: Emergency Department

GCS: Glasgow Coma Scale

ICU: Intensive Care Unit

MMSE: Mini-Mental Scale Examination

NDRS: New Delirium Rating Scale

RASS: Richmond Agitation-Sedation Scales

DECLARATIONS

Ethics approval and consent to participate: Approval of the ethics committee with **……..** decision number has been taken from the **….. Ethics Committee for Non-Interventional Clinical Investigations** for the prospective, observational study. Written informed consents were obtained from study participants.

Consent for publication: Not applicable

Availability of data and material: The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Each author approved the submitted version

MB: design of the work, interpretation of data, analysis the data, have drafted the work

AB: interpretation of data, analysis the data, have drafted the work

EO: interpretation of data, analysis the data, have drafted the work

MMK: design of the work, analysis the data, have drafted the work

NMA: design of the work, have drafted the work, substantively revised it

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