



**Original Article**

**Malnutrition, Sepsis, and Tumor Lysis Syndrome Are Associated with Increased Rate of Acute Mortality in Mature B Cell Non-Hodgkin Lymphoma in a Pediatric Population-Study from Tertiary Care Hospital in Pakistan**

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**Competing interests:** The authors have declared that no competing interests exist.

**Abstract. Background:** Outcomes of pediatric mature B cell non-Hodgkin's lymphoma in resource-challenged countries are negatively affected by an increased rate of early and toxic deaths. Aim of this study is to assess the rate of acute mortality and define significant risk factors present in children with mature B cell non-Hodgkin's lymphoma.

**Methods:** A retrospective analysis was done of patients with B cell non-Hodgkin's lymphoma from January 2012 till December 2016. Risk factors studied for acute mortality were malnutrition, stage, prior surgery with open laparotomy, lactate dehydrogenase levels, tumor lysis syndrome, sepsis, and fungal infection

**Results:** A total of 233 patients were enrolled in the study. Eighty-five (36.4%) were below 15<sup>th</sup> percentile weight for age. Treatment was started in 226 patients. Eighty-eight percent of children showed a 20% response after COP pre-phase. Tumor lysis syndrome was developed in 20.6% (n = 48) children and 42.9% (n = 100) patients had sepsis, 71/100 patients had culture-proven sepsis. 19.7% (n = 46) patients developed fungal infection. There was 19.7% (n = 46) acute mortality. The most common cause of death was sepsis (n = 22, 47.8%) followed by acute renal failure secondary to tumor lysis syndrome. On multivariate analysis, three independent variables found significant for early death are malnutrition, sepsis, and tumor lysis syndrome.

**Conclusion:** Rate of acute mortality in mature B cell NHL is high in our set up and significant risk factors are tumor lysis syndrome, sepsis, and malnourishment at the time of presentation.

**Keywords:** Mature B cell non-Hodgkin lymphoma, Acute mortality, Sepsis, Malnutrition, Tumor lysis syndrome.

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**Introduction.** Non-Hodgkin Lymphoma is the fifth most common malignancy in children less than 15 years of age, B cell non-Hodgkin's Lymphoma being the most common immunophenotype.<sup>1</sup>

With modern intensive multi-agent chemotherapy protocols adopted after several consecutive international trials, a five years survival for B cell non-Hodgkin's Lymphoma has reached up to 80 – 90 % in

the developed world. However, in low-income countries such as Pakistan results are not so promising due to delay in seeking medical care, improper and delayed referral system, low socio-economic status and lack of awareness.<sup>2</sup> Furthermore, factors such as malnutrition, and lack of supportive care lead to reduced tolerance to chemotherapy. These factors together have a negative impact on prognosis.<sup>3-6</sup> Cunha

Group A	Completely resected stage I Completely resected abdominal stage II
Group B	Unresected stage I & II disease Resected stage II disease other than abdominal completely resected tumors Stage III disease
Group C	Any CNS involvement and/or bone marrow involvement > 25%

Group A	COPAD → COPAD
Group B	COP → COPADM1 → COPADM 2 → CYM 1 → CYM 2
Group C	COP → COPADM1 → COPADM2 → CYVE 1 → CYVE2 → M1 → M2 → M3 → M4

COP (cyclophosphamide, vincristine, prednisolone), COPADM (cyclophosphamide, vincristine, prednisolone, adriamycin, methotrexate), CYM (cytarabine, methotrexate), CYVE (cytarabine, etoposide and high dose ara-C)

**Figure 1.** Risk group stratification according to UKCCSG 2003 guidelines and treatment according to risk groups.

et al. in his studies reported 26.7% mortality in Brazil as compared to 2.6% in developed countries.<sup>7</sup>

We conducted this study to assess the rate of acute mortality and define significant risk factors present in children with B cell non-Hodgkin's Lymphoma treated in a tertiary care hospital in Pakistan.

**Methods.** Retrospective chart review of all children less than 18 years of age treated at Shaukat Khanum Memorial Cancer Hospital & Research Centre (SKMCHRC) for B-cell Non-Hodgkin's Lymphoma from January 2012 to December 2016 was done.

Data were collected for age, gender, residence, nutritional status, duration of symptoms, site, stage, Lactate dehydrogenase levels, treatment, complications, and outcomes. The diagnosis was made on morphology and immunohistochemistry. Patients were classified according to World Health Organization classification.

Staging done according to St. Jude Children Research Hospital staging system with CT scan.<sup>9</sup> Central nervous system positive disease was defined as any L3 blasts in cerebrospinal fluid, cranial nerve palsy (if not explained by extra-cranial tumor), clinical spinal cord compression, isolated intracerebral mass or parameningeal extension: cranial and/or spinal. Bone marrow with less than 25% blasts was considered positive. Stage I and II were labeled as Low stage and III and IV as Advanced stage. Patients were risk stratified in Treatment Groups A, B, and C based on staging and resection status according to United Kingdom Children's Cancer Study Group 2003 guidelines (**Figure 1**).

All patients were treated according to the UKCCSCG 2003 Non-Hodgkin's lymphoma guidelines. Cytoreductive chemotherapy COP was given according to guideline recommendations. In clinically unstable patients, a second COP was also given. Reassessment scans were done on day 7 of COP in treatment groups B and C and therapy was intensified from Group B to C if there was less than 20% response. Tumor lysis syndrome preventive protocol was followed in all patients at risk.

Acute mortality was defined as death before administration of the second induction course

COPADM cycle 2. Risk factors studied for acute mortality were malnutrition, stage, prior surgery with open laparotomy, lactate dehydrogenase levels, tumor lysis syndrome, sepsis, and fungal infection. Malnutrition was assessed using World Health Organization weight for age percentile charts and patients were divided in three groups, less than 3<sup>rd</sup>, 3<sup>rd</sup> to 15<sup>th</sup> and more than 15<sup>th</sup> centiles.<sup>10</sup> Tumor lysis syndrome (TLS) was defined according to Cairo-Bishop definition as any two of the following features: Uric acid level > 8 mg/dl or 25% increase from baseline, Potassium level > 6 meq/l or 25% increase from baseline, Phosphorus > 6.5 mg/dl, Calcium level < 7 mg/dl or 25% decrease from baseline, and clinical if laboratory criteria fulfilled plus any of these three: serum creatinine > 1.5 normal upper limit for age, arrhythmias or sudden death and seizures.<sup>11</sup> Sepsis was considered to be present either based on the presence of positive blood cultures or labeled in clinical notes if culture is negative. Fungal infection was considered if proven histologically; biochemical markers were elevated or if the probable fungal infection was labeled and treated in clinical notes based on radiographic findings.

Statistical analysis was carried out using the SPSS software (version 20.0; SPSS, Chicago, IL, USA). Continuous variables were stated as Mean ± SD, and categorical variables were computed as frequencies and percentages. Categorical variables were compared using the chi-square test or Fisher's exact test (when necessary). The continuous variables were compared using the independent t-test. Multivariable logistic regression (MLR) model was used to identify the independent risk factors associated with mortality. Statistical significance was defined as a two-tailed p-value < 0.05.

## Results.

**Clinical Characteristics.** A total of 237 patients were registered with B-cell non-Hodgkin's lymphoma between January 2012 and December 2016. Four patients refused treatment and were excluded from the study. Therefore 233 patients were included in the study with mean age and standard deviation of

**Table 1.** Descriptive Statistics\*.

VARIABLES	CHARACTERISTICS	FREQUENCY N (%)
Age(in years)	Mean ± standard deviation	7.36 ± 4.01
Gender	Male	166(71.2%)
	Female	67 (28.8%)
Area of Resident	Punjab	81 (34.8%)
	Sindh	3 (1.3%)
	Balochistan	3 (1.3%)
	Khyber Pakhtunkhawa	105 (45.1%)
	Afghanistan	41 (17.6%)
Nutritional Status	Less than 3 <sup>rd</sup> Centile	46 (19.7%)
	3 – 15	39 (16.7%)
	More than 15	148 (63.5%)
Diagnosis	Burkitt Lymphoma	161 (69.1%)
	DLBCL*	64 (27.5%)
	B-Cell NHL NOS	8 (3.4%)
Type of surgeries	Biopsy	96 (41.2%)
	Laparotomy	137 (58.8%)
Fungal Infection	No	183 (78.5%)
	Yes	46 (19.7%)
	Missing	4 (1.7%)
Sepsis	No	129 (55.4%)
	Yes	100 (42.9%)
	Missing	4 (1.7%)
TLS	No	182 (78.1%)
	Yes	48 (20.6%)
	Missing	3 (1.3%)
LDH	Mean ± SD*	1873.96 ± 3417.54
Stage	Lower stage	44 (18.9%)
	Advance stage	189 (81.1%)

\*Diffuse large B cell Lymphoma

7.34±4.01 years. **Table 1** shows the clinical characteristics of patients. Majority of participants were male (n = 166, 71.2%). The largest number belonged to Khyber Pakhtunkhwa (n = 105, 45.1%), while 41 patients (17.6%) were from Afghanistan. Forty-six children (19.7%) were below the third percentile. Three diagnoses encountered were Burkitt’s lymphoma, Diffuse Large B cell Lymphoma and B cell Lymphoma not otherwise specified. Burkitt’s lymphoma was the most frequent diagnosis (n = 166, 69.1%). Mean duration of symptoms at the time of presentation was 3.17 ± 2.6 months. The most common site of the presentation was the abdomen. Two patients presented with jaw disease. A total of 137 patients had laparotomy at the time of presentation, 89 patients came with enterostomies. Most of the patients presented with advanced stage with stage III being the most frequent (n = 132, 56.7%). Bone marrow involvement was seen in 30 patients, and central nervous system positive disease was observed in 36

patients.

*Treatment.* Three patients had resected disease entirely, two of them presented after seven to eight months of resection and one after one year. After discussion in a multidisciplinary team meeting, no chemotherapy was given in these patients. All three were disease free at the time of analysis. Four patients expired before treatment. One presented with infected open laparotomy wound and sepsis. Other three were in spontaneous tumor lysis syndrome. Three patients were treated as Group A, 174 as Group B and 49 as Group C. Thirteen patients have upstaged from Group B to C after COP day 7 re-evaluation. Two hundred three patients were given cytoreductive COP chemotherapy, 2<sup>nd</sup> COP was given in 32 patients. Re-evaluation scans after COP 1 were done in 193 patients, and 170 out of 193 patients had more than 20% response after COP 1. **Figure 2** shows treatment and outcome in the study cohort.

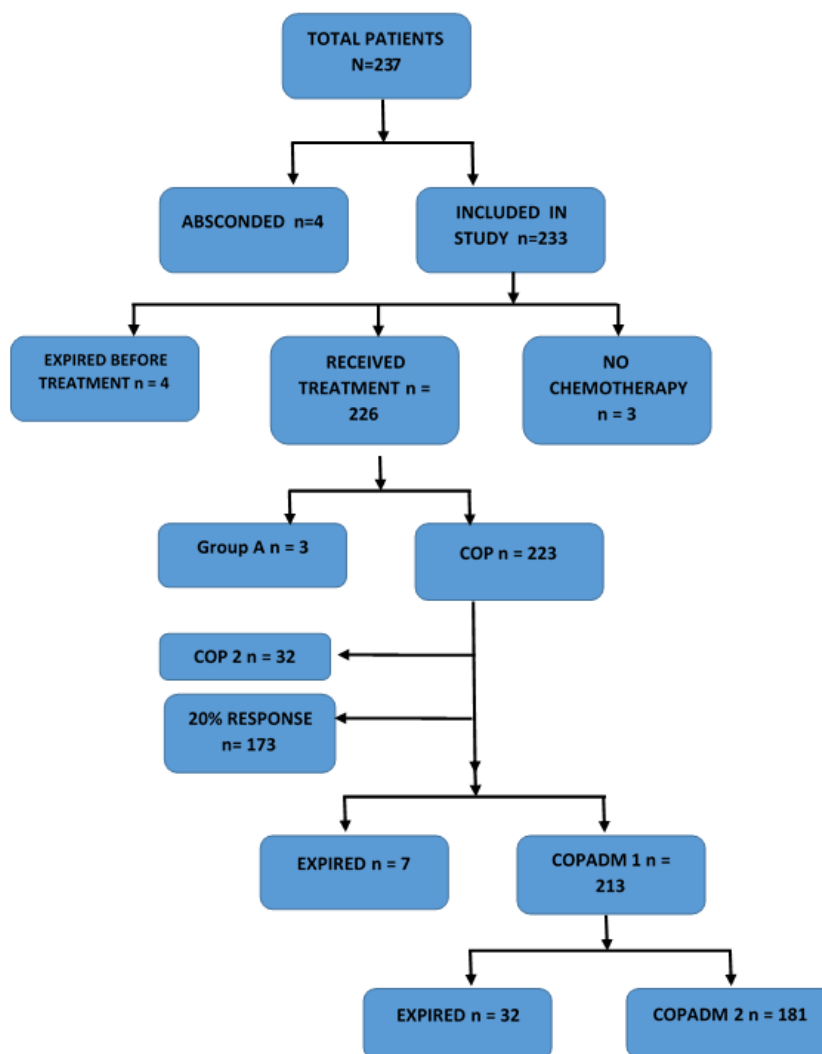


Figure 2. Algorithm showing treatment and outcomes in enrolled patients.

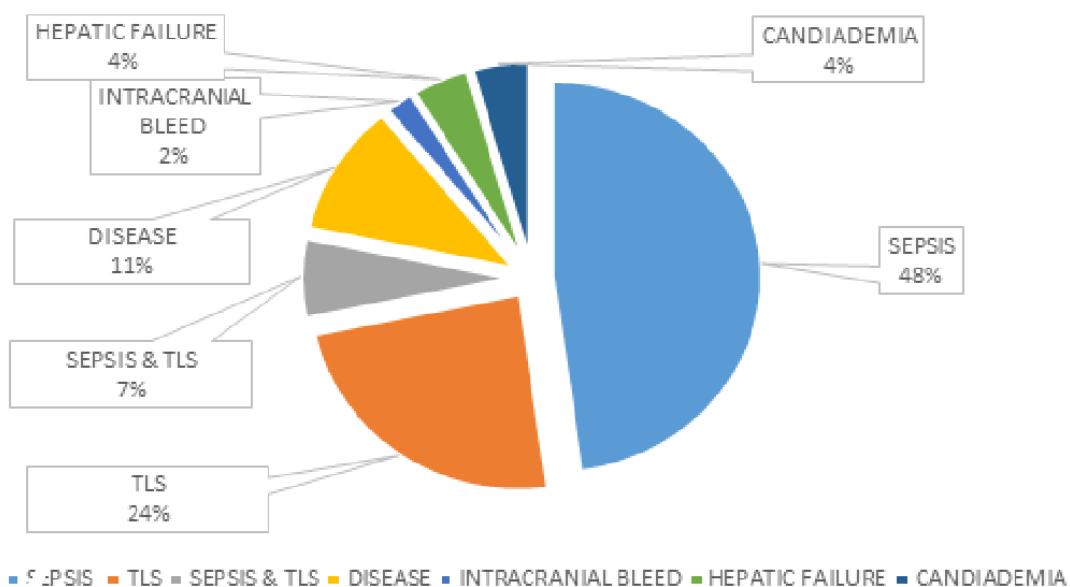


Figure 3. Causes of death.

**Outcomes and Complications.** Tumor lysis syndrome was developed in 20.6% (n=48) children, uric acid ranged from 8 - 41 mg/dl, phosphorus 6 - 18 mg/dl. Renal replacement in the form of hemodialysis was done in 24 patients. Rasburicase became available in hospital in 2016 and was given to 11 patients. 42.9% (n = 100) patients had sepsis, 71/100 patients had culture proven sepsis. Gram-negative bacilli were isolated in 64 patients. 19.7% (n = 46) patients developed fungal infection.

There was 19.7% (n = 46) acute mortality. Sepsis remained the most common cause of death (n = 22, 47.8%) followed by acute renal failure secondary to tumor lysis syndrome (**Figure 3**).

There is a statistically significant association between nutritional statuses, fungal infection, sepsis, tumor lysis syndrome, stage, lactate dehydrogenase with outcome variable death before COPADM cycle 2 (**Table 2**). In multivariable analysis, three independent variables were identified as significant independent risk factors for early death: nutritional statuses; 3-15 centile (adjusted odds ratio [AOR] 5.18; 95% confidence interval [CI] 1.80-15.14), p-value (0.003) and less than 3 centile (adjusted odds ratio [AOR] 5.50; 95% confidence interval [CI] 1.83-15.60), p-value (0.002). Likewise, sepsis (AOR 7.50; 95% CI (2.30-24.41), 0.001), TLS (AOR 7.84; 95% CI (3.16-19.44), 0.001) as shown in **Table 3**.

**Discussion.** Non-Hodgkin lymphomas in children are high grade and aggressive tumors.<sup>1</sup> Prognosis in the

developed world has improved steadily over the last two decades with overall survival reaching up to 80 - 90%. Outcomes are inferior in low-income countries. Increased rate of early and toxic deaths contribute to low survival rates in these countries. Our study revealed a 19.7% acute mortality. Similar rate (22.2%) was reported in a study from Brazil. In a study from Iraq, 22.6% Patients died before a second induction course.

On the other hand, Patte C et al. in his study reported overall mortality as low as 2.8% and no early death.<sup>4,5,7,12</sup> We analyzed various factors including stage, TLS, sepsis, fungal infection, prior surgery and malnutrition to identify risk factors responsible for this high rate of early deaths in a curable disease. Response to chemotherapy in our population was adequate, 88% of patients showed > 20% reduction in disease on COP Day 7 re-evaluation.

General characteristics of our study population were the same as reported in the literature. Majority of our patients were male similar to other studies.<sup>12-16</sup> Mean age was seven years as reported in the literature (6.2 ± 2.8 years).<sup>17</sup> The most frequent site of presentation in most studies is abdomen which is also the case in our study.<sup>12,15,16</sup> Burkitt's lymphoma is the most common diagnosis in previous studies; our results confirm this finding. Most patients presented with an advanced stage which is similar to data available.<sup>2,12,15,16</sup> On multivariate analysis, we found sepsis, tumor lysis syndrome and malnutrition as significant.

Sepsis remained the most common cause of death,

**Table 2.** Bivariate Analysis.

Variables	Characteristics	Death prior to COPADM 2		
		NO 187 (80.3%)	YES 46 (19.67%)	
Age in (years)	Mean ± SD*	7.48 ± 4.01	6.87 ± 4.04	0.35
Sex	Male	134 (80.7%)	32 (19.3%)	0.87
	Female	53 (79.1%)	14 (20.9%)	
Nutritional Status	Less than 3rd Centile	29 (63.0%)	17 (37.0%)	0.001
	3-15	22 (56.4%)	17 (43.6%)	
	More than 15	136 (91.9%)	12 (8.1%)	
Type of surgeries	Biopsy	78 (81.2%)	18 (18.8%)	0.90
	Laparotomy	109 (79.6%)	28 (20.4%)	
Fungal Infection	No	157 (85.8%)	26 (14.2%)	0.001
	Yes	28 (60.9%)	18 (39.1%)	
Sepsis	No	125 (96.9%)	4 (3.1%)	0.001
	Yes	60 (60.0%)	40 (40.0%)	
TLS	No	167 (91.8%)	15 (8.2%)	0.001
	Yes	18 (37.5%)	30 (62.5%)	
Stage	Lower stage	43 (97.7%)	1 (2.3%)	0.001
	Advance stage	144 (76.2%)	45 (23.8%)	
LDH	Mean ± SD*	1418.87 ± 2446.02	3724.02 ± 5579.02	0.001

\*Standard deviation.

**Table 3.** Risk Factors.

Variables	Characteristics	Unadjusted OR (CI), p-value	Adjusted OR (CI), p-value
Nutritional Status	More than 15 Centile	Ref	Ref
	3-15 Centile	6.64 (2.90 15.40), 0.001	5.18 (1.80 15.14), 0.003
	Less than 3 centile	8.76 (3.70 20.81), 0.001	5.50 (1.83 15.60), 0.002
Sepsis	No	Ref	Ref
	Yes	20.83 (7.12 60.91), 0.001	7.50 (2.30 24.41), 0.001
TLS	No	Ref	Ref
	Yes	18.56 (8.44 40.80), 0.001	7.84 (3.16 19.44), 0.001
Type of surgeries	Biopsy	Ref	Ref
	Laparotomy	0.90 (0.46 1.74), 0.75	1.17 (0.47 2.90), 0.73
Stage	Lower stage	Ref	Ref
	Advance stage	13.44 (1.80 100.36), 0.01	3.20 (0.36 28.11), 0.30

although timely and aggressive supportive care was provided to all patients. Gram-negative bacilli were isolated in 90% of culture-positive patients. The most common causative organism was *E. coli*, which was multidrug resistant in 20% of patients. A study from Iraq also identified infection significantly associated with mortality in the early phase.<sup>12</sup> Overwhelming sepsis in our study population may be due to malnutrition, surgeries, and admissions in peripheries. This high rate of infection and multidrug-resistant septicemia emphasize the need for strict infection control measures and hospital-based antibiotic surveillance programs.

Malnutrition remains a severe problem in resource poor countries. 19.7% of our population was below the 15<sup>th</sup> percentile and 16.7% between 3<sup>rd</sup> to 15<sup>th</sup> percentiles. Risk of acute mortality increased with decreasing nutrition status. The same situation was seen in our neighboring country, where 35% of the study population was malnourished, and it was found an independent risk factor for inferior EFS.<sup>14</sup> Malnutrition is associated with decreased treatment tolerance, inadequate response to chemotherapy, increased risk of infection and reduced quality of life. This supports the need to assess the nutritional status of all children immediately after admission and make an individualized nutritional care plan. Early recognition of the need for parenteral nutrition, tube feeding and involvement of the parents in the rehabilitation process will be helpful. All of these steps have already been implemented in our institute after data analysis and preliminary results of this study.

Tumor lysis syndrome was reported in 48 children with uric acid ranging from 8 - 40 mg/dl, phosphorous 6 – 18 mg/dl, hyperkalemia, and renal failure. Cunha et al. found high uric acid levels and tumor lysis syndrome to be associated with adverse outcome.<sup>7</sup> Forty percent of these children had spontaneous tumor lysis syndrome; most of them presented with extensive disease and fell into stage III. Fifty-two percent

progressed to clinical tumor lysis syndrome despite adherence to prophylactic protocol, monitoring, and management. Rasburicase was given to 11 patients only because of availability issue. There is evidence of rasburicase preventing renal failure and improving GFR if given prior to cytoreductive chemotherapy in high risk patients.<sup>18</sup>

Non-Hodgkin's lymphoma treatment has evolved over the last four to five decades towards a more conservative surgical approach and intensive chemotherapy.<sup>17</sup> We have observed 137 out of 143 patients with abdominal disease had laparotomy done at the time of presentation; 65% of these patients had either ileostomy or colostomy. Although statistically not proved to be a significant risk factor laparotomy in itself carries increased mortality in the form of infectious risk, difficulty in nutritional rehabilitation secondary to enterostomies and mechanical obstruction due to adhesions. Mechanism of bacterial translocation and sepsis after gut surgery in immunocompromised patients has been described in the literature. In our study also, organisms isolated were similar to healthy gastrointestinal flora.<sup>19</sup>

Mean duration of symptoms was 3.17 months which given the aggressive and rapidly multiplying nature of the tumor is too long. Thus, children presented with bulky disease and advanced stage. Economic issues, social beliefs and lack of awareness are important factors which we think contributed to delayed presentation to the primary physician. Insufficient diagnostic facilities in primary and secondary health care centers in distant parts of the country where most patients come from, along with the long traveling distance from referring hospital and residential issues make it more difficult for families to reach oncology centers on time.

There is a need for extensive multicenter studies in Pakistan and make collaborative efforts to develop an adaptive risk protocol for patients presenting in a moribund condition. The modifications should allow

nutritional rehabilitation, better management of tumor lysis syndrome especially spontaneous tumor lysis syndrome and infections, thus reducing toxic deaths in the early phase. As discussed by Fadoo Z. et al., children in developing countries may benefit from less intensity, risk-based protocol.<sup>20</sup> Government and non-government organizations should make policies for improving infrastructure, providing better radiological and pathological services for early diagnosis and timely referral. Most important is the education of parents to seek medical care early and primary health physicians

and surgeons to follow less invasive approach and communicate with oncologist where necessary. Survival outcomes can be significantly improved with an integrated approach between primary health physicians, surgeons, and oncologists in case of suspected malignancy.

**Conclusions.** Rate of acute mortality in B cell Non-Hodgkin's lymphoma is high in our set up, and significant risk factors are tumor lysis syndrome, sepsis and malnourishment at time of presentation.

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