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Sepsis as a cause of death among elderly cancer patients: an updated SEER database analysis 2000-2021

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Background: Sepsis is an aggressive response to an infection leading to widespread inflammation, and may lead to death. It remains a significant challenge for cancer patients especially for the elderly due to their immunocompromised status and other comorbidities. So, this study aimed to assess the risk of mortality due to sepsis among elderly cancer patients and provide an updated evidence to the literature for better management outcomes.

Methods: We used data from the Surveillance, Epidemiology, and End Results (SEER) program. We included cancer patients who died due to sepsis between 2000 and 2021. The Standardized Mortality Ratio (SMR) for elderly cancer patients who died due to sepsis was calculated as observed/expected (O/E). We used 95% confidence intervals (CI) and the excess risk (ER) was per 100 000. Significance was achieved at 0.05.

Results: Out of 5 239 194 elderly cancer patients, 18 311 died from sepsis. Men represented 55% and the majority were Caucasians (82%). Death from sepsis along 10+ years of follow-up had a significant SMR with an O/E of 1.32 (P >0.05, 95% CI: 1.30-1.34, ER = 2.56) especially within the first year after cancer diagnosis (O/E = 3.00, P >0.05). Gastric cancer had an increased risk for sepsis death in the elderly (O/E = 2.55, P < 0.05, 95% CI: 2.28-2.85). Liver and intrahepatic bile cancer had a significant SMR for sepsis (O/E = 5.56, P < 0.05, 95% CI: 5.01-6.36). However, it had an insignificant risk for sepsis deaths along 120 + months of follow-up period (O/E = 1.21, 95% CI: 0.25-3.52, ER = 1.73).

Conclusion: Sepsis is a rapid silent killer targeting a vulnerable population. Although it had a declining mortality rate along 10 + years of follow up as the majority die due to other cancer-related and non-cancer-related causes, it still represents a certain threat to elderly cancer patients due to the immunosuppression of cancer treatment regimen and antibiotic resistance. Further studies are encouraged to focus on elderly cancer patients' health care and to intensify infection control measures.

Keywords: cancer, elderly, mortality, SEER, sepsis

Background

Sepsis is the biological response to an infection, resulting in a widespread inflammation, tissue damage, and organ failure and eventually leads to death[1]. Sepsis is a major concern because it affects about 1.7 million people annually in the U.S., and cancer

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HIGHLIGHTS

- Sepsis remains a significant challenge for cancer patients especially for the elderly due to their immunocompromised status and other comorbidities.
- Although the risk of sepsis-related mortality declined over the years, it was a major cause of death in elderly cancer patients with significant SMR over 10+ years of follow-up after diagnosis.
- There was increased risk for sepsis-related death in gastric cancer with the peak significant risk in the first year of diagnosis.
- Surgical management had reduced sepsis mortality compared to patients treated medically.

patients represent 13.6% of them. The incidence of sepsis in patients with cancer is approximately ten times greater than in the non-cancer population[2,3]. Among sepsis-related deaths, approximately 21% are linked to solid tumors, and 10% to hematologic cancers. These cases often involve comorbidities and delayed recognition or treatment[1,4]. The risk of mortality varies by cancer type and age with the most frequent sepsis source including the respiratory and genitourinary tract infection.

Cancer care has progressed over the past decades. However, morbidity and mortality are still increasing among cancer patients

either due to the aggressive and prolonged treatment regimen with severe adverse effects or the cancer itself increasing death susceptibility[5]. Sepsis remains a significant challenge for the survival of cancer patients especially for elderly cancer patients emphasizing the need for preventive measures, early diagnosis, and prompt treatment[6].

A recent study showed hospital mortality for severe sepsis for cancer patients was 52% higher compared to non-cancer patients and had five times greater hospital mortality than mild or moderate sepsis in cancer. This corresponds to a national estimate of 46 729 hospitalized severe sepsis deaths annually among cancer patients[7]. So, this study aimed to assess the risk of mortality due to sepsis among elderly cancer patients.

Methods

Data source

This a retrospective cohort study based on the Surveillance, Epidemiology, and End Results (SEER) database that included ~26.5% of the general US population. We used the database of SEER, 17 Registries (excl AK), Nov 2023 Sub (2000-2021) for SMRs[8]. The database consists of anonymized data for public use. The study has been reported in line with the STROCSS criteria[9]. The study required no patients' consent or ethical approval and was registered at ClinicalTrials.gov with **ID NCT06619535**[10].

Study population

We included all cancer patients who died due to sepsis diagnosed between 2000 and 2021. We included cancer patients with only malignant behavior and sequence 0 or 1. Sequence 0 indicated the patient had only one cancer record while sequence 1 indicated the patient may had developed many cancer records following the first one. We selected patients aged 65 or more according to the most recent WHO classification for the elderly age group[11]. We excluded patients diagnosed with autopsy only or death certificate only.

Statistical analysis

We analyzed the baseline characteristics with different variables: gender, race (White, Black, and others), marital status (married, unmarried, and unknown), year of diagnosis. Tumor characteristics included: SEER grade (Grade I: well differentiated; Grade II: moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated and unknown), stage (in situ, localized, Regional, distant, unknown), and the use of surgery, chemotherapy, and radiotherapy. We compared sepsis as a cause of death (COD) between different primary sites and cancer types: oral cavity and pharynx, digestive system, respiratory system, bones and joints, soft tissue including heart, skin excluding basal and squamous, breast, female genital system, male genital System, urinary System, eye and orbit, brain and other nervous system, endocrine system, lymphoma, myeloma, leukemia.

The SEER* Stat software 8.3.8 was used for data extraction and analysis. The Standardized Mortality Ratio (SMR) for elderly cancer patients who died due to sepsis was calculated as O/E across 10+ years of follow-up after the primary diagnosis with many intervals <1-year, 1-5 years, 5-10 years, and 10+ years. The observed cancer patients who died from sepsis while the expected population included the general population who died from sepsis. We used 95% confidence intervals (CI) and the excess risk (ER) was per 10 000. Significance was achieved at 0.05. With further analysis, we compared death due to sepsis with both cancer causes and non-cancer causes among elderly cancer patients.

Results

Out of 5 239 194 elderly cancer patients, 18 311 died from sepsis as shown in Table 1. Men represented 55% and women represented 45% with the majority being Caucasians (82%). About 30% were diagnosed with localized tumors, 19% had distant spread while only 14% had regional spread. Most patients performed cancer-directed surgery, due to which there was a reduction in mortality compared to patients who had no surgical intervention (51.7% and 35.9 %). The majority received no radiotherapy (77.3%) nor chemotherapy (81.4%) as adjuvant therapy and they survived more than those who received adjuvant treatment as a part of their management plan (21.4% and 18.5% respectively). Patients with grade IV cancer had a higher rate of death (30.7%).

Death from sepsis along 10+ years of follow-up had a significant SMR with an O/E of 1.32 (P <0.05, 95% CI: 1.30-1.34, ER = 2.56) especially within the first year after cancer diagnosis (O/E = 3.00, P <0.05) as shown in Table 2. The total number of unmarried patients who died from sepsis was greater compared to the married with an O/E of 239.86 (P < 0.05, 95% CI: 234.62-245.18, ER = 2421.97), especially within the first year after cancer diagnosis (O/E = 539.10, P < 0.05, 95% CI: 519.2-559.6, ER = 4621.50). Patients who were diagnosed after 2021 had an increased risk to die from sepsis with an O/E of 2319.81 (P < 0.05, 95% CI: 2197.79-2446.84, ER = 22 825.84) especially in the first year after cancer diagnosis with O/E of 5050.00 (P < 0.05, 95% CI: 4530.38-5612.87, ER = 35221.80). The risk of death from sepsis was greater in patients who received chemotherapy with an O/E of 354.67 (P < 0.05, 95% CI: 342.86-366.79, ER = 2770.03), especially within the first year after cancer diagnosis (O/E = 816.96, P < 0.05, 95% CI: 772.75-863.05, ER = 4818). Patients who received no radiotherapy had an O/E of 229.49 (P < 0.05, 95% CI: 342.86-366.79, ER = 2296.39) with a significant increase in the first year after cancer diagnosis (O/E = 534.63, P < 0.05, 95% CI: 519.50-550.08, ER = 4419.22). Patients who received medical treatment without surgical intervention had a significantly increased risk of dying from sepsis along 10+ years of follow-up (O/E = 244.10 (P < 0.05, 95% CI: 238.23-250.07, ER = 2527.75) compared to who had surgical intervention (O/E = 695.78, P < 0.05, 95% CI: 669.44-722.89, ER = 5630).

As shown in Table 3, although the risk of death from sepsis declined over the following years, it was a major cause of death in patients with an overall O/E of 1.32 (P > 0.05, 95% CI: 1.30-1.34, ER = 2.56) while during the 10+ years of follow-up, there was statistically insignificant risk of death due to sepsis (O/E = 1.02, P > 0.05, 95% CI: 0.99-1.06). However, death due to cancer causes had also highly significant SMR in elderly cancer patients within 10+ years of follow-up (O/E = 7.23, P < 0.05, 95% CI: 7.22-7.24) especially within the first year after diagnosis (O/E = 27.02, P < 0.05, 95% CI: 26.96-27.08). Although it was declining over the following years as shown in Fig. 1, it had

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Table 1

Baseline characteristcs of elderly cancer patients died from sepsis along 10+ years of follow-up after diagnosis

Characteristic	All deaths			<1 year		1-5 years		5-10 years		>10 years	
	N	No. of patients (%)	Mean age at death	N	Mean age at death	N	Mean age at death	N	Mean age at death	N	Mean age at death
Overall	18 311		81.24	1866.29	77.88	5761	80.12	4045	83.26	2900	87.14
Gender											
Male	10 102	55	80.85	2956	77.32	3222	79.73	2258	82.77	1666	86.69
Female	8209	45	81.72	2649	78.51	2539	80.61	1787	83.88	1234	87.74
Race											
White	14 958	82	81.57	4458	78.13	4695	80.42	3354	83.55	2451	87.32
Black	2565	14	79.41	857	76.63	827	78.37	552	81.67	329	85.52
Other	788	43	80.85	290	77.71	239	80.22	139	82.52	120	87.79
Marital status											
Married	8582	47	80.61	2409	76.7	2547	78.86	2015	82.58	1611	86.79
Unmarried	7972	43.5	81.69	2764	78.8	2593	81.03	1595	84	1020	87.58
Unknown	1757	9.5	82.27	432	78.64	621	81.52	435	83.7	269	87.5
Stage											
In situ	1076	5.8	83.55	124	80.39	430	82.1	354	84.44	168	87.74
Localized	5513	30	81.63	1146	78.44	1921	80.15	1569	83.16	877	86.31
Regional	2577	14	79.56	1011	77.12	855	79	498	82.56	213	86.41
Distant	3508	19	78.59	1822	76.89	1134	78.98	437	82.92	115	85.32
Unknown	1076	5.8	81.08	628	79.88	308	82.05	105	83.58	35	86.69
Grade											
Grade I	1375	7.5	82.45	209	78.08	470	80.2	381	83.33	315	87.64
Grade II	4840	26.4	82.25	931	78.21	1366	79.95	1399	83.11	1144	87.25
Grade III	3252	17.7	81.19	813	77.3	980	79.73	840	82.73	619	86.52
Grade IV	563	30.7	80.13	215	78.07	205	79.56	94	82.44	49	87.17
Surgery											
No surgery	6581	35.9	80.3	2630	77.28	1951	79.83	1112	82.83	888	87.1
Surgery	9474	51.7	82.04	2024	78.18	3004	80.16	2559	83.48	1887	87.2
Unknown	154	2.8	81.39	33	78.64	64	80.97	37	82.28	20	85.65
Radiotherapy											
Yes	3935	21.4	80.5	804	75.55	1208	78.1	1028	81.83	895	86.66
No	14 170	77.3	81.45	4732	78.28	4483	80.67	2979	83.76	1976	87.34
Chemotherapy											
No	14 907	81.4	82.06	4329	78.83	4561	81.03	3445	83.6	2572	87.28
Yes	3404	18.5	77.63	1276	74.67	1200	76.66	600	81.28	328	86
Sepsis	18 311	1	81.24	5605	77.88	5761	80.12	4045	83.26	2900	87.14
Year of diagnosis											
2000-2005	2191	11.9	79.29	1269	78.5	886	80.32	36	82.1	0	
2006-2010	3530	19.2	80.46	1182	78.28	1397	80.48	916	83.11	35	84.03
2011-2015	4869	26.5	81.59	1246	78.03	1469	80.18	1378	83.73	776	86.17
2016-2020	6369	34.7	81.99	1564	77.24	1683	79.86	1444	83.15	1678	87.58
2021+	1352	7.3	81.6	344	76.63	326	79.12	271	82.07	411	87.42

a significant lower risk of death within one to five years of follow-up (O/E = 5.93, *P* < 0.05, 95% CI: 5.92-5.95). However, a 10 + years of follow-up had an O/E of 1.73 (*P* < 0.05, 95% CI: 7.22-2.24). In addition, non-cancer causes represented a highly significant SMR among elderly cancer patients (O/E = 1.08, *P* < 0.05) especially within the first year of diagnosis (O/E = 1.71, *P* < 0.05, 95% CI: 1.70-1.72).

The most common cancer sites in elderly patients who died due to sepsis are shown in Fig. 2. Along 10+ years of follow-up, there was increased risk for sepsis death in gastric cancer (O/E = 2.55, *P* < 0.05, 95% CI: 2.28-2.85) as shown in Table 4, with the peak significant risk in the first year of diagnosis (O/E = 5.69, *P* < 0.05, 95% CI: 4.85-6.63, ER = 33.08) while the one to five years of follow-up period had an O/E of 1.65 (*P* < 0.05, 95% CI: 1.30-2.05, ER = 4.74). However, the overall risk had an O/E of 2.55 (*P* < 0.05, 95% CI: 0.97-2.26, ER = 5.82). Esophageal cancer had increased risk of total deaths from sepsis (O/E = 3.91, *P* < 0.05, 95% CI: 3.37-4.52) with significantly higher risk of death in all time intervals from the first year of follow-up period (O/E = 6.37, *P* < 0.05, 95% CI: 5.14-7.80, ER = 34.29) until 10+ years of follow-up period (O/E = 2.41, *P* < 0.05, ER = 16.37). Liver and intrahepatic bile cancer had a significant SMR for sepsis (O/E = 5.56, *P* < 0.05, 95% CI: 5.01-6.36). However, it had an insignificant risk for sepsis deaths along 120+ months of follow-up period (O/E = 1.21, 95% CI: 0.25-3.52, ER = 1.73). In brain cancer of elderly patients, the O/E for sepsis was 5.22 (*P* < 0.05, 95% CI: 4.15-6.47) with the highest risk during the first year after diagnosis (O/E = 7.11, *P* < 0.05, ER = 32.39). Thyroid cancer had an insignificant risk for total sepsis death in elderly cancer patients (O/E = 0.85, *P* < 0.05, ER = –0.95). In addition, the risk of death

Table 2

The standardized mortality ratio (SMR) for sepsis as a cause of death for cancer patients calculated as observed/expected (O/E) based on patients' characteristics

	<1 year		1-5 years		5-10 years		>10 years		Overall	
	O\E (95% CI)	ER	O\E (95% CI)	ER	O\E (95% CI)	ER	O\E (95% CI)	ER	O\E (95% CI)	ER
Gender										
Male	449.28*(433.23–465.77)	3668.57	165.37*(159.71–171.18)	1512.94	146.54*(140.56–152.72)	1659.46	193.08*(183.92–202.58)	2891.62	201.64*(197.73–205.61)	2074.58
Female	568.83*(547.37–590.91)	4190.30	186.66*(179.47–194.07)	1536.78	175.23*(167.20–183.55)	1744.86	241.78*(228.47–255.65)	2912.93	244.60*(239.34–249.95)	2200.93
Race										
White	517.39*(502.32–532.81)	3769.91	181.79*(176.63–187.07)	1492.48	162.78*(157.32–168.39)	1674.48	214.41*(206.01–223.07)	2887.82	225.01*(221.42–228.64)	2084.43
Black	362.1*(338.26–387.18)	4354.46	125.89*(117.45–134.77)	1673.07	123.9*(113.77–134.68)	1893.74	165.7*(148.28–184.61)	2978.74	166.81*(160.41–173.39)	2348.68
Other	1144.45*(1016.51–1284.04)	4950.24	346.32*(303.80–393.13)	1687.54	254.17*(213.68–300.11)	1540.75	379.93*(315.00–454.30)	2956.71	436.27*(406.34–467.82)	2381.76
Marital status										
Married	498.11*(478.41–518.41)	3478.05	165.55*(159.18–172.10)	1338.58	150.79*(144.28–157.52)	1570.20	203.56*(193.74–213.74)	2820.03	206.80*(202.45–211.22)	1929.73
Unmarried	539.10*(519.19–559.58)	4621.50	185.28*(178.21–192.55)	1742.18	166.66*(158.58–175.04)	1837.14	224.51*(210.94–238.72)	3008.55	239.86*(234.62–245.18)	2421.97
Unknown	339.34*(308.09–372.89)	2933.54	167.63*(154.70–181.35)	1589.14	162.74*(147.80–178.77)	1863.91	210.99*(186.53–237.77)	3006.35	196.85*(187.75–206.27)	2041.49
Stage										
In situ	142.15*(118.23–169.48)	1229.12	151.85*(137.84–166.90)	1471.93	189.81*(170.55–210.65)	2177.78	312.74*(267.24–363.77)	4323.77	176.21*(165.84–187.06)	1810.89
Localized	309.49*(291.83–327.94)	2391.21	165.91*(158.58–173.50)	1436.27	180.76*(171.92–189.93)	1960.81	305.22*(285.35–326.10)	4148.75	205.44*(200.06–210.94)	1949.88
Regional	750.24*(704.70–797.95)	5312.21	249.25*(232.82–266.53)	2024.44	228.67*(209.03–249.67)	2284.29	338.32*(294.41–386.93)	3974.76	339.74*(326.75–353.12)	2915.83
Distant	1125.96*(1074.85–1178.88)	8434.88	354.23*(333.91–375.46)	2951.21	283.60*(257.93–311.48)	2922.06	397.22*(327.95–476.80)	4625.69	527.53*(510.21–545.28)	4530.71
Unknown	1120.66*(1034.72–1211.84)	10940.98	292.29*(260.56–326.82)	2959.10	213.51*(174.63–258.47)	2568.11	453.57*(315.93–630.81)	6098.64	492.88*(463.87–523.24)	5175.07
Grade										
Grade I	227.99*(198.12–261.08)	1680.75	149.88*(136.64–164.06)	1262.18	150.37*(135.65–166.25)	1565.64	223.21*(199.24–249.28)	2858.82	171.93*(162.96–181.26)	1617.53
Grade II	293.35*(274.81–312.82)	2202.97	123.02*(116.58–129.72)	1058.51	143.49*(136.07–151.21)	1542.45	193.79*(182.72–205.36)	2740.78	161.71*(157.18–166.33)	1594.27
Grade III	388.40*(362.16–416.04)	2981.66	147.83*(138.72–157.38)	1277.37	154.70*(144.41–165.52)	1651.27	223.43*(206.18–241.75)	3122.70	192.17*(185.62–198.89)	1862.74
Grade IV	655.78*(571.05–749.55)	5084.39	270.74*(234.94–310.45)	2273.43	204.68*(165.40–250.47)	2102.32	230.44*(170.48–304.65)	3098.78	320.44*(294.52–348.04)	2918.59
Surgery										
No surgery	695.78*(669.44–722.89)	5630.15	189.38*(181.07–197.97)	1739.10	135.95*(128.08–144.18)	1563.90	188.96*(176.74–201.81)	2899.42	244.10*(238.23–250.07)	2527.75
Surgery	328.23*(314.08–342.85)	2475.07	151.35*(145.99–156.86)	1286.96	160.59*(154.43–166.93)	1669.16	220.56*(210.72–230.74)	2869.60	187.58*(183.83–191.40)	1773.94
Unknown	314.17*(216.26–441.21)	2490.03	219.13*(168.76–279.83)	1952.92	191.35*(134.73–263.75)	2003.81	243.75*(148.89–376.45)	3379.74	228.99*(194.25–268.15)	2187.45
Radiotherapy										
Yes	356.06*(331.87–381.55)	2291.26	161.89*(152.89–171.29)	1227.83	147.25*(138.39–156.53)	1488.05	204.12*(190.96–217.94)	2826.82	186.62*(180.83–192.54)	1680.59
No	534.63*(519.50–550.08)	4419.22	177.19*(172.05–182.46)	1624.65	162.23*(156.45–168.16)	1783.83	214.03*(204.69–223.68)	2929.40	229.49*(225.72–233.30)	2296.39
Chemotherapy										
No	447.46*(434.23–461.00)	3689.98	156.27*(151.77–160.87)	1411.66	150.91*(145.91–156.03)	1653.10	207.86*(199.91–216.05)	2897.38	201.27*(198.06–204.53)	2022.37
Yes	816.96*(772.75–863.05)	4818.68	307.78*(290.61–325.70)	2175.64	215.99*(199.05–233.99)	1993.79	241.35*(215.94–268.94)	2926.55	354.67*(342.86–366.79)	2770.03
sepsis	3.00*(2.93–3.08)	12.84	1.12*(1.10–1.15)	0.88	0.99(0.96–1.02)	–0.08	1.02(0.99–1.06)	0.27	1.32*(1.30–1.34)	2.56
Year of diagnosis										
2000-2005	298.95*(282.72–315.86))	2378.30	104.59*(97.82–111.71)	907.74	109.46*(76.66–151.54)	1106.97	0	0	167.96*(161.00–175.15)	1422.82
2006-2010	373.27*(352.29–395.17)	2888.51	118.87*(112.72–125.27)	1039.44	97.02*(90.84–103.51)	1013.09	155.52*(108.32–216.29)	1874.76	143.58*(138.88–148.40)	1320.71
2011-2015	528.65*(499.70–558.84)	4075.37	168.45*(159.94–177.29)	1482.40	127.99*(121.32–134.93)	1409.35	119.35*(111.10–128.05)	1603.53	171.77*(166.98–176.66)	1766.51
2016-2020	1117.27*(1062.57–1174.04)	8671.15	418.69*(398.92–439.18)	3647.41	2681.70*(277.89–308.30)	3138.95	248.58*(236.83–260.76)	3507.41	372.42*(363.33–381.68)	4031.74
2021+	5050.00*(4530.38–5612.87)	35221.80	2681.70*(2398.46–2398.46)	21363.13	1966.35*(1739.18–2214.94)	19259.90	1609.84*(1457.95–1773.26)	20411.63	2319.81*(2197.79–2446.84)	22825.84

*Significant, P < 0.05.
ER: excess risk per 10,000.

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Table 3

The standardized mortality ratio (SMR) for sepsis as a cause of death (COD) compared to cancer other non-cancer causes across different time intervals in elderly cancer patients

	Sepsis COD		Cancer cause COD		Non-cancer COD	
	O/E (95% CI)	ER	O/E (95% CI)	ER	O/E (95% CI)	ER
1 year	**3.00[*] (2.93-3.08)**	12.84	**27.02[*] (26.96-27.08)**	2,639.67	**1.71[*] (1.70-1.72)**	238.32
1-5 years	**1.12[*] (1.10-1.15)**	0.88	**5.93[*] (5.92-5.95)**	533.21	**0.96[*] (0.95-0.96)**	−15.57
5-10 years	0.99 (0.96-1.02)	−0.08	**2.34[*] (2.32-2.35)**	167.84	**0.98[*] (0.98-0.98)**	−9.94
10+ years	1.02 (0.99-1.06)	0.27	**1.73[*] (1.71-1.74)**	110.5	**1.04[*] (1.03-1.04)**	30.46
Overall	**1.32[*] (1.30-1.34)**	2.56	**7.23[*] (7.22-7.24)**	733.44	**1.08[*] (1.08-1.08)**	35.32

[*]Significant, $P < 0.05$.
ER: excess risk per 10 000.

at different time intervals for each site of cancer in elderly patients who died due to sepsis showed no specific pattern of decline or rise. However, gastric, liver, and pancreatic cancer showed a declining SMR over the following 10+ years after diagnosis.

Table 4

The standardized mortality ratio (SMR) for sepsis as a cause of death for elderly cancer patients stratified by the primary cancer site across different time intervals of follow-up after cancer diagnosis

|	0-11 months		12-59 months		60-119 months		120+ months		Total	
	O/E (95% CI)	Excess risk	O/E (95% CI)	Excess risk	O/E (95% CI)	Excess risk	O/E (95% CI)	Excess risk	O/E (95% CI)	Excess risk
All site	**3.00[*] (2.93-3.08)**	12.84	**1.12[*] (1.10-1.15)**	0.88	0.99 (0.96-1.02)	−0.08	1.02 (0.99-1.06)	0.27	**1.32[*] (1.30-1.34)**	2.56
Colorectal	**4.42[*] (4.14-4.71)**	25.13	**1.21[*] (1.13-1.31)**	1.71	**1.16[*] (1.07-1.26)**	1.56	1.11 (1.00-1.23)	1.35	**1.61[*] (1.55-1.67)**	5.45
Esophagus	**6.37[*] (5.14-7.80)**	34.29	**3.38[*] (2.60-4.32)**	15.68	**1.99[*] (1.20-3.11)**	8.29	**2.41[*] (1.24-4.20)**	16.37	**3.91[*] (3.37-4.52)**	20.83
Stomach	**5.69[*] (4.85-6.63)**	33.08	**1.65[*] (1.30-2.05)**	4.74	**1.58[*] (1.16-2.10)**	5.13	1.52 (0.97-2.26)	5.82	**2.55[*] (2.28-2.85)**	12.38
Liver and intrahepatic bile	**9.06[*] (7.74-10.54)**	42.94	**4.41[*] (3.57-5.38)**	17.99	**2.05[*] (1.12-3.45)**	6.62	1.21 (0.25-3.52)	1.73	**5.65[*] (5.01-6.36)**	25.71
Pancreas	**7.31[*] (6.43-8.27)**	40.61	**2.74[*] (2.12-3.49)**	10.92	**2.49[*] (1.56-3.78)**	12.24	1.74 (0.64-3.79)	8.19	**4.88[*] (4.37-5.42)**	25.94
Lung and Bronchus	**4.75[*] (4.44-5.07)**	23.39	**1.64[*] (1.49-1.80)**	4.2	**1.48[*] (1.27-1.71)**	3.92	**1.67[*] (1.34-2.05)**	7.31	**2.54[*] (2.42-2.67)**	10.72
Breast	1.01 (0.89-1.14)	0.06	**0.78[*] (0.72-0.84)**	−1.4	**0.85[*] (0.79-0.92)**	−1.19	0.92 (0.85-1.01)	−0.79	**0.86[*] (0.82-0.90)**	−1.04
Prostate	**0.81[*] (0.72-0.91)**	−1.16	**0.74[*] (0.70-0.79)**	−1.79	**0.76[*] (0.71-0.81)**	−2.22	**0.89[*] (0.83-0.95)**	−1.49	**0.79[*] (0.77-0.82)**	−1.78
Kidney and Renal Pelvis	**2.81[*] (2.37-3.31)**	10.84	**1.27[*] (1.09-1.46)**	1.77	**1.25[*] (1.05-1.48)**	2.16	1.18 (0.92-1.48)	2.06	**1.46[*] (1.34-1.59)**	3.49
Urinary Bladder	**2.56[*] (2.29-2.86)**	12.09	**1.22[*] (1.11-1.34)**	1.87	1.12 (0.99-1.26)	1.22	**1.31[*] (1.14-1.51)**	4.06	**1.40[*] (1.32-1.48)**	3.69
Brain	**7.11[*] (5.40-9.19)**	32.39	**3.68[*] (2.18-5.81)**	13.7	1.13 (0.14-4.07)	0.89	**4.46[*] (1.21-11.41)**	33.44	**5.22[*] (4.15-6.47)**	23.33
Thyroid	0.80 (0.40-1.44)	−0.91	0.74 (0.52-1.03)	−1.37	**0.67[*] (0.45-0.96)**	−2.32	1.31 (0.93-1.78)	3.04	0.85 (0.70-1.02)	−0.95
Uteri	**2.58[*] (2.11-3.11)**	8.08	**1.24[*] (1.05-1.46)**	1.38	1.09 (0.90-1.31)	0.65	1.12 (0.90-1.38)	1.21	**1.33[*] (1.21-1.45)**	2.21
Melanoma	**0.63[*] (0.50-0.78)**	−2.44	**0.69[*] (0.61-0.77)**	−2.3	**0.77[*] (0.68-0.87)**	−2.13	0.88 (0.76-1.02)	−1.42	**0.74[*] (0.69-0.80)**	−2.16
Anus and Anorectum	**3.79[*] (2.40-5.69)**	16.39	**1.78[*] (1.18-2.58)**	4.95	1.07 (0.55-1.87)	0.55	0.61 (0.17-1.56)	−4.31	**1.69[*] (1.31-2.15)**	4.98
Oral cavity and pharynx	**4.65[*] (3.85-5.57)**	20.98	**1.51[*] (1.21-1.86)**	3.12	**1.68[*] (1.29-2.15)**	5.34	1.38 (0.90-2.02)	4.04	**2.10[*] (1.87-2.35)**	7.54
Lymphoma	**3.48[*] (3.08-3.92)**	16.38	**1.28[*] (1.13-1.44)**	2	1.07 (0.92-1.25)	0.63	**1.25[*] (1.03-1.51)**	2.84	**1.53[*] (1.43-1.64)**	4.27
Leukemia	**3.56[*] (3.04-4.13)**	18.27	**1.62[*] (1.40-1.86)**	4.71	**1.35[*] (1.11-1.64)**	3.2	0.93 (0.65-1.29)	−0.79	**1.78[*] (1.63-1.94)**	6.48

[*]$P < 0.05$.
ER: excess risk per 10 000.
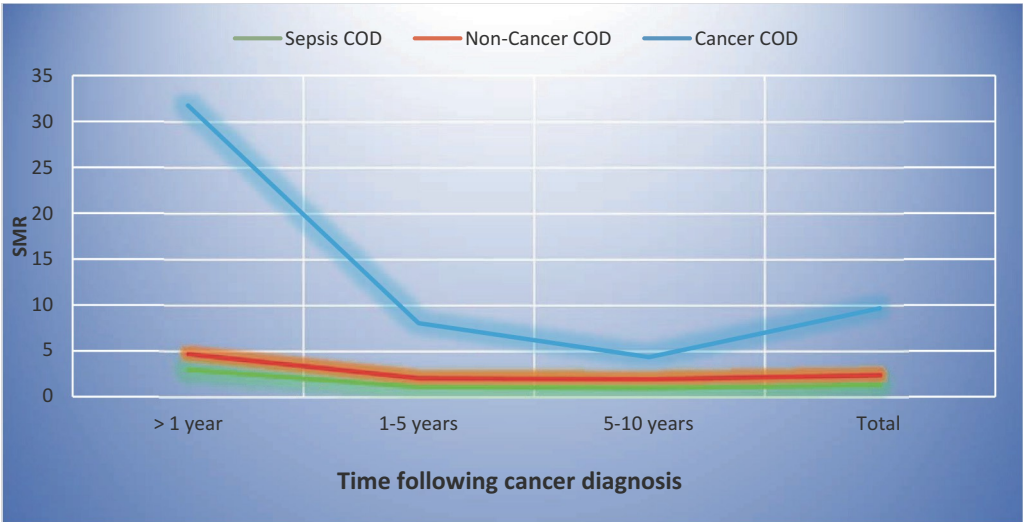
Figure 1. Shows the standardized mortality ratio (SMR) for sepsis as a cause of death (COD) compared to cancer and non-cancer COD along 10+ years of follow-up.

Discussion

Sepsis is a significant challenge for cancer survivors contributing to mortality and morbidity, especially in elderly patients. They are more vulnerable due to their immunocompromised state after cancer treatment besides other age-related comorbidities. Healthcare improvement has raised the expectation regarding a probable decrease in the incidence of sepsis-related death among cancer patients. However, elderly patients are prone to have other comorbidities such as advanced disease stage, chemotherapy-induced neutropenia, and frequent hospitalization leading to poorer sepsis outcomes[12-15]. Thus, this is the first study quantifying the burden of sepsis-related death in elderly cancer patients.

Cancer is considered a major risk factor for sepsis-related mortality. Williams *et al* noted a 52% higher risk of mortality among cancer patients compared to non-cancer patients who acquired sepsis[7]. Similarly, Angus *et al* reported a mortality rate of 43% with severe sepsis in patients with distant cancer, which was higher than any other comorbidity[16]. In this study, we found that over a 10+ year follow-up, elderly cancer patients had a significantly increased risk for sepsis mortality, especially within the first year after diagnosis (SMR = 3.00). Surgical management had reduced sepsis mortality compared to patients treated medically (35.9% and 51.7%), while chemo(radio)therapy was associated with higher risk due to their immunosuppressive systemic side effects. Similarly, Shvetsov *et al* found
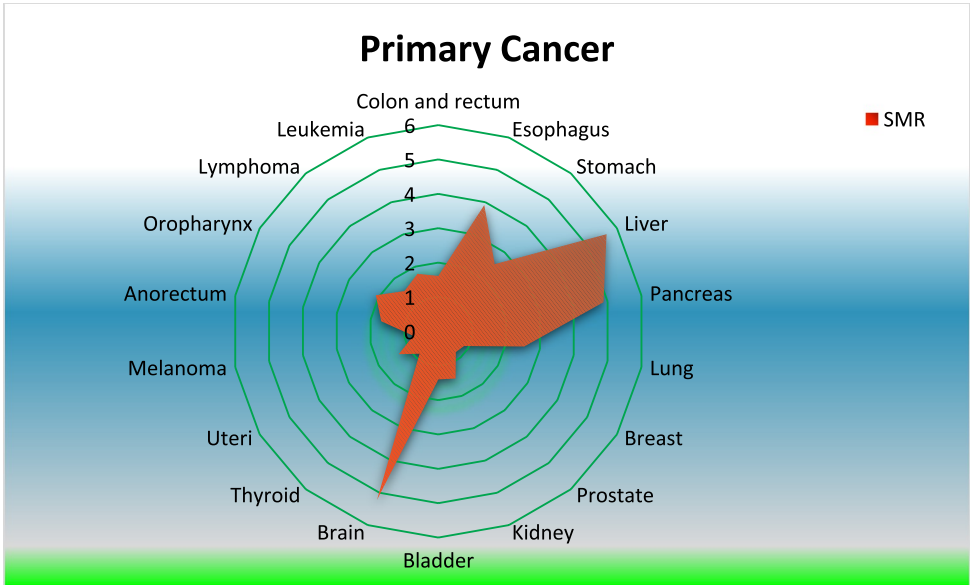

Figure 2. Shows the standardized mortality ratio (SMR) for sepsis among elderly cancer patients in different primary cancer sites.

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chemotherapy was a major contributor to sepsis mortality across multiple cancer types, particularly gastrointestinal and hepatobiliary malignancies, due to the major risk of infection-related complications[17]. Unmarried patients showed significant sepsis mortality, potentially reflecting social factors and treatment delays[18-21]. This observation is supported by another study highlighting the role of marital status and social support in improving treatment outcomes and reducing mortality risks among cancer patients[22]. Cancer primary sites such as the esophagus, stomach, and liver had the highest sepsis risk, a trend consistent with the findings of Shvetsov et al[17]. who identified gastrointestinal cancers as carrying particularly high infection-related mortality risks. However, we observed a decline in sepsis mortality over the past two decades as cancer-related deaths predominated.

The strength of this study lies in its large, population-based sample of elderly cancer patients, which enhances the generalizability of findings. This is the first study focusing on quantifying sepsis-related mortality in elderly cancer patients. The SEER database provides comprehensive data on cancer type, stage, grade, and treatment, enabling robust analyses of factors affecting outcomes. Moreover, its decades-long follow-up data allow for detailed survival analysis and insights into long-term outcomes. However, the retrospective nature of this study represents a weakness point, it is subjected to selection bias and lacks randomization. Additionally, the SEER database lacks data about chemotherapy regimens or dosages, potential confounding factors and comorbidities like other chronic diseases, smoking and life style beside the broad definitions of some clinical variables that may lead to imprecision in comparisons.

Conclusion and recommendations

Chemotherapy and medical treatment with no surgical intervention represented a serious risk for the elderly cancer patient due to their immunosuppressive side effects and systemic complications. Although sepsis had an increased mortality rate among elderly cancer patients, cancer-related and the other non-cancer causes of death also represented a threat due to the multiple other comorbidities for this vulnerable population. These results highlight the necessity for regular early infection screening as a prophylactic measure that would benefit sepsis management protocols for elderly cancer patients, prompt intervention, and preventive strategies like vaccinations, hygiene practices, and monitoring for infections are essential to reduce the risk of sepsis-related mortality and improve treatment outcomes for these vulnerable population. We encourage more studies to focus on elderly cancer patients' health care and intense infection control measures in the era of antibiotic resistance[14].

Ethical approval

Ethical approval was not required for this study as it was a retrospective SEER based study and the data are anonymized and publicly available. However, the protocol was registered at Clinicaltrail.gov with identification number of ID NCT06619535.

Consent

Informed written consent was not required for this study as it was SEER based which conceal patients' personal data and the data were anonymous.

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Author's contribution

I.E.: conceptualization, data-analysis, writing, study design, revision; H.E.: writing, figures and tables creation; S.E.: interpreting findings, writing; B.A.: writing and revision; A.E.: supervision, data extraction, editing and revision. All authors revised and approved the submitted version of the manuscript.

Conflicts of interest disclosure

No conflicts of interest to declare.

Guarantor

Asmaa Ellaithy and Ibrahim Ellaithy.

Research Registration Unique Identifying Number (UIN)

The study was registered at Clinicaltrial.gov with identification number of ID NCT06619535 (https://clinicaltrials.gov/study/NCT06619535#more-information).

Provenance and peer review

Not invited.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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