

Serum CA242: a biomarker for diagnosis, progression, and metastasis in multiple tumors

Kaicheng Shen

Army Medical University

Xiangquan Qin

Army Medical University

Xingxing Su

Army Medical University

Yishi Yang

Army Medical University

Hongqian Wang

Army Medical University

Haisu Dai

Army Medical University

Yan Jiang

Army Medical University

Jie Bai

Army Medical University

Zhiyu Chen (✉ chenzhiyu_umn@163.com)

Army Medical University

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Abstract

Background

CA242 is a classic biomarker used for diagnosing digestive tract tumors, especially pancreatic cancer. However, CA242 serum levels in some tumor patients and what might influence these levels remain unknown or uncertain. This study aimed to reveal the pancancer landscape of serum CA242 levels and identify some influencing factors.

Methods

In the current study, serum CA242 levels and clinical information, including clinical stage and metastatic status, were collected from 37,493 patients with 35 different types of neoplastic disease, and CA242 values were also obtained for 880 healthy controls.

Results

Serum CA242 levels in patients with one of 21 different cancers were significantly higher than those in healthy controls and had diagnostic value in 9 tumors (AUC > 0.7, P < 0.05); serum CA242 levels were increased across all malignant digestive tract tumors. Compared to patients without metastasis, cancer patients with one of 15 kinds of cancer with lymph node metastasis and distant metastasis showed elevated CA242 levels. Moreover, CA242 was helpful in distinguishing the clinical stage and metastatic status in 6 cancers. In addition, the presence of multiple metastases and liver metastasis might result in increased CA242 levels.

Conclusions

Overall, CA242 can not only serve as a diagnostic biomarker for malignant tumors in the digestive system but also predict the progression, stage, and metastasis of many other tumors that have not received clinical attention.

Background

Currently, cancer is one of the most critical public health problems worldwide[1]. To improve therapeutic outcomes, identifying cancer patients in an early stage or precisely diagnosing the clinical stage and metastatic status is essential. Therefore, finding useful biomarkers is crucial.

CA242 is a sialylated carbohydrate antigen that was isolated in 1985[2]; it attaches to core proteins/lipids detected on the cell surface or in serum[3]. Subsequently, the serum level of CA242 was reported to be increased in tumor patients with pancreatic cancer[4–8]. CA242 was found to be overexpressed more strongly in pancreatic carcinoma cells than in adjacent tissues[4]. Moreover, its expression correlates with the degree of differentiation and clinical stage[4, 9]; however, CA242 tumor expression does not have any relationship with serum levels[4]. Interestingly, the serum CA242 level is scarcely affected by cholestasis and benign obstructive jaundice, while its sensitivity and specificity are similar to those of CA19-9 and CA50[7]. Hence, it is believed that serum CA242 is a product of cancer cells[10, 11].

Currently, although CA242 has been used as a first-line clinical marker of pancreatic cancer for more than a decade[11], research on it has continued. CA242 is not merely a diagnostic predictor[12, 13] but also participates in forecasting the progression and prognosis of many tumors[14–16]. In pancreatic cancer, colorectal cancer[17–19], gastric cancer[20, 21] and other tumors and when used alone or in combination with CA19-9, CA50, CEA and other biomarkers[4, 7, 14, 22–24], CA242 is gradually becoming better understood and applied more broadly. Therefore, CA242 is routinely included in screening and monitoring many different cancers.

However, there are few comprehensive in-depth studies on the pancancer CA242 atlas across a variety of tumors. Except for in pancreatic cancer, colorectal cancer and some other tumors, we have no understanding of the potential of the serum CA242 level in patients with tumors, and no systematic comparison has been performed until now. Therefore, we conducted a retrospective study of serum CA242 levels in 37,493 patients with 35 different defined neoplastic diseases and 880 healthy controls who visited the clinical laboratory of our hospital in the past five years.

Methods

Patients

All data for the detection of CA242 in the past five years were collected from the Medical Big Data and Artificial Intelligence Center of SouthWest Hospital, the First Affiliated Hospital of the Army Medical University. Serum CA242 values for 37,493 patients suffering from 35 benign or malignant tumors and 880 healthy controls were measured and analyzed. All patients were definitively diagnosed, and in some patients, the extent of the tumor, including the lymph node metastasis (LNM) status, distant metastasis (DM) status, and TNM staging according to the American Joint Commission on Cancer (AJCC), was recorded. Rapid ethical approval was acquired, and all methods followed the relevant guidelines and regulations.

Assays

The detection of serum CA242 in all patients was performed by the Laboratory Department of the First Affiliated Hospital of the Army Medical University. Serum CA242 levels were quantified by the TESMI™ Tumor Marker Panel (7 markers) (flow cytometry fluorescence method) (Shanghai Tellgen Cooperation, Shanghai, China) according to the manufacturer's instructions. The technical platform and instrument were the Tellgen Super Multiplex Immunoassay (TESMI) F3999 system. The cutoff value for serum tumor markers recommended by the kit was 20 U/mL for CA242.

Statistical analysis

All data were processed with Microsoft Excel (Microsoft, Inc., USA). All the original data were imported, cleaned, and collated by MySQL version 8.0.15 (Oracle Corporation), Navicat version 12.0.29, and Python version 3.7.2 (Python Software Foundation). Statistical analysis was performed by using SPSS version 23. Due to the data having a nonnormal distribution, the Kruskal-Wallis test was used for statistical analysis, and Dunn's multiple-comparisons test was used for performing multigroup comparisons. Enumerative data were compared with the chi-square test. The prediction value was calculated by receiver operating characteristic (ROC) curve analysis. Then, the area under the curve (AUC) was calculated, and the largest value of the Youden index was chosen as the cut off. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The serum CA242 levels of 37,493 patients with 35 types of tumors and 880 healthy controls were statistically compared and analyzed, and the results are shown in Table 1. To visualize the results, we constructed Fig. 1 and ranked all the diseases from highest to lowest according to the median CA242 level.

Table 1
 Characteristics and serum CA242 levels of patients and healthy c

	Count			Age		p value	Mean(SD)	Medin(25%,75%)	P value	Fold change	AL
	Case	Female	Male	Female	Male						
Total	38373	18618	19755	49.76	44.11	0.35	21.143(37.53)	8.06(4.05,33.95)	-	-	-
Healthy control	880	397	483	57.86	55.98	0.08533	5.58(4.56)	4.32(2.46,7.26)	-	-	-
Pancreatic cancer	650	260	390	60.06	60.65	0.52500	94.28(120.54)	35.08(8.51,142.23)	< 0.0001	8.12037037	0.8
Gallbladder carcinoma	193	125	68	60.18	60.90	0.67000	78.64(113.50)	24.94(6.94,98.67)	< 0.0001	5.773148148	0.8
Cholangiocarcinoma	856	355	501	62.46	62.70	0.77600	77.22(117.85)	20.68(7.18,85.93)	< 0.0001	4.787037037	0.8
Colorectal cancer	4486	1677	2809	59.84	61.18	0.00100	26.50(59.58)	8.39(4.78,497.4)	< 0.0001	1.940972222	0.7
Mediastinal Cancer	8	0	8	0.00	55.80	-	41.97(88.92)	12(8.95,15.34)	0.0777	2.777777778	0.8
Periampullary carcinoma	83	31	52	57.45	57.88	0.87500	47.87(93.24)	11.66(4.21,36.35)	< 0.0001	2.699074074	0.7
Testicular cancer	16	0	16	0.00	52.60	-	36.24(93.67)	9.01(4.69,21.81)	0.0772	2.085648148	0.8
Ovarian cancer	1211	1211	0	51.17	0.00	-	19.52(42.27)	8.12(4.4,16.13)	< 0.0001	1.87962963	0.7
Vaginal cancer	24	24	0	52.67	0.00	-	21.19(44.67)	8.11(5.38,14.67)	0.0012	1.876157407	0.8
Ureter cancer	12	12	0	61.80	0.00	-	28.59(42.75)	8.05(4.74,26.99)	0.1396	1.862268519	0.8
Neuroendocrine carcinoma	25	14	11	49.36	58.45	0.06000	12.16(22.90)	7.33(3.87,10.02)	0.4501	1.696759259	0.8
Gastric cancer	2015	635	1380	57.28	61.39	< 0.0001	28.03(66.02)	7.26(4.07,15.54)	< 0.0001	1.680555556	0.8
Nasonasopharyngeal carcinoma	811	219	592	49.30	51.46	0.00900	11.05(16.97)	7.05(4.02,12)	< 0.0001	1.631944444	0.8
Gastric cardia adenocarcinoma	24	5	19	64.40	65.89	0.80400	36.25(60.54)	7.045(4.23,23.92)	0.0012	1.876157407	0.8
Craniofacial malignant tumour	395	112	283	57.83	59.21	0.32500	10.10(19.92)	6.68(3.77,10.11)	< 0.0001	1.546296296	0.8
Cervical cancer	2169	2169	0	51.29	0.00	-	11.54(23.97)	6.62(4.02,11.58)	< 0.0001	1.532407407	0.8
Endometrial cancer	438	438	0	55.63	0.00	-	11.70(17.66)	6.59(3.95,11.47)	< 0.0001	1.525462963	0.8
Lung cancer	7536	2538	4998	59.78	62.36	< 0.0001	18.49(45.97)	6.48(3.67,12.9)	< 0.0001	1.5	0.8
Breast cancer	3824	3824	0	50.94	0.00	-	9.57(16.15)	6.24(3.72,10.51)	< 0.0001	1.443287037	0.8
Vulvar cancer	52	52	0	53.05	0.00	-	7.82(6.38)	6.17(3.69,11.19)	0.2174	1.428240741	0.8
Fallopian Tube Cancer	10	10	0	61.80	0.00	-	7.01(4.62)	6.01(3.65,10.15)	> 0.9999	1.391203704	0.8
Renal Cell Cancers	902	333	569	57.80	58.40	0.51800	12.93(38.40)	5.39(3.13,9.98)	< 0.0001	1.246527778	0.8
Laryngocarcinoma	333	24	309	58.75	62.48	0.08300	6.79(6.35)	5.29(2.91,8.85)	0.1694	1.224537037	0.8
Lymphoma	33	16	17	50.69	55.76	0.37300	8.91(12.53)	5.25(3.12,10.09)	> 0.9999	1.215277778	0.8

SD standard deviation

	Count		Age							ROC	
Liver cancer	4347	711	3636	56.76	55.31	0.00400	17.09(47.40)	5.22(3.15,9.785)	< 0.0001	1.208333333	0.9
Esophagus cancer	1328	272	1056	64.05	63.88	0.76600	10.95(35.79)	5.14(3.15,8.66)	< 0.0001	1.188657407	0.9
Prostatic cancer	727	0	727	0.00	73.06	-	9.27(20.47)	5.12(3.16,8.94)	< 0.0001	1.185185185	0.9
Skin cancer	194	91	103	65.09	62.47	0.16800	6.18(4.65)	5.02(3.20,7.85)	> 0.9999	1.162037037	0.9
Bladder cancer	602	114	488	62.75	66.49	0.00300	9.26(21.00)	4.83(3.07,8.28)	0.0225	1.118055556	0.9
Thyroid cancer	3477	2625	852	45.72	45.28	0.38700	6.83(10.67)	4.79(2.93,8.07)	0.0143	1.108796296	0.9
Cervical intraepithelial neoplasias	107	107	0	45.19	0.00	-	6.19(4.81)	4.74(2.94,8.15)	> 0.9999	1.097222222	0.9
Penile cancer	65	0	65	0.00	56.40	-	5.3(4.41)	4.01(2.51,7.1)	> 0.9999	0.928240741	0.9
Leukemia	504	206	298	41.97	43.59	0.33200	6.32(7.33)	4(2.37,7.68)	> 0.9999	0.925925926	0.9
Benign colorectal neoplasms	21	7	14	62.86	58.29	0.44800	7.10(8.33)	3.85(2.70,8.22)	> 0.9999	0.891203704	0.9
Thymic cancer	15	4	11	45.75	60.09	0.08600	6.54(6.31)	3.58(2.70,8.46)	> 0.9999	0.828703704	0.9
SD standard deviation											

The mean and median serum CA242 levels of most patients with malignant disease were significantly higher than those of the healthy controls, and the serum CA242 levels of all the patients with malignant digestive tract malignant tumors were increased. Compared to the healthy controls, the tumor patients with the most significantly increased median levels were those with pancreatic cancer (8.12-fold), gallbladder cancer (5.77-fold), or cholangiocarcinoma (4.78-fold). However, the patients with fallopian tube cancer, lymphoma, penile cancer, leukemia, benign colorectal neoplasms, or thymic cancer were not significantly different from the healthy controls (Fig. 1 and Fig. 2).

To test the capacity of CA242 to diagnose tumors, we made ROC curves for all the diseases. The cancers with a value greater than 0.8 were pancreatic cancer (0.8616), cholangiocarcinoma (0.8349), and gallbladder carcinoma (0.8145). In addition, the AUCs of colorectal cancer (0.7268), testicular cancer (0.7165), ovarian cancer (0.7053), vaginal cancer (0.7604), ureteral cancer (0.7323) and cardiac cancer (0.7604) were all greater than 0.7 (Table 1).

CA242 in different metastatic situations

Serum CA242 levels varied widely in most diseases; for example, the median value for colorectal cancer was 8.39, but the quartile range was from 4.78 to 497.4 (Table 1 and Fig. 1). We speculated that a factor such as the progression of the disease might affect the levels, so we divided the tumor patients into three groups according to their metastatic situation: no metastasis (NM), LNM, and DM.

We found that the mean and median serum CA242 levels were increased in most tumor patients who exhibited LNM or DM compared to those who exhibited NM. The diseases that showed the most significant increases in the serum CA242 level were cholangiocarcinoma [median (quartile) for NM: 17.79 (6.77, 65.95), LNM: 76.03 (16.39, 204.02), and DM: 34.01 (12.24, 120.94)]; gallbladder carcinoma [NM: 8.125 (3.66, 37.28) and DM: 36.85 (11.84, 159.89)]; periampullary carcinoma [NM: 6.31 (3.76, 27.07) and DM: 19.56 (11.37, 110.625)]; and pancreatic cancer [NM: 22.71 (6.97, 95.74) and DM: 57.66 (17.42, 189.06)]. Additionally, endometrial cancer and colorectal cancer showed levels that increased approximately two fold, and CA242 levels increased significantly in patients with metastasized cancer, including those with lung cancer, cervical cancer, liver cancer, bladder cancer, breast cancer, esophageal cancer, or craniofacial malignant tumor. In contrast, the median in vulvar cancer patients with LNM was 3.49 (3.1, 4.47), which was significantly lower than that in patients with NM [7.99 (4.45, 12.25)] (Table 2).

Table 2
Serum CA242 in different metastatic situations

	Count			Age		median(SD)	Median(25%,75%)	p value		ROC
	Case	Female	Male	Female	Male			Control vs	NM vs.	AUC(95% confidence interval)
Nasopharyngeal carcinoma										
NM	323	95	228	49.98	52.25	10.94(19.18)	6.81(3.76,11.66)	< 0.0001	-	0.6509(0.6154, 0.6865)
LNM	323	92	231	48.86	50.30	11.12(12.67)	7.12(4.10,13.85)	< 0.0001	0.556	0.6824(0.6387, 0.7261)
DM	165	32	133	48.59	52.09	11.12(19.60)	7.23(4.37,11.15)	< 0.0001	> 0.9999	0.6809(0.6466, 0.7152)
Cholangiocarcinoma										
NM	693	286	407	62.95	63.57	67.89(109.21)	17.79(6.77,65.95)	< 0.0001	-	0.8198(0.7979, 0.8416)
LNM	95	39	56	60.54	59.00	129.45(145.77)	76.03(16.39,204.02)	< 0.0001	< 0.0001	0.9076(0.867, 0.94)
DM	68	30	38	60.23	58.82	99.34(137.81)	34.01(12.24,120.94)	< 0.0001	0.0409	0.8882(0.8372, 0.9391)
Gallbladder carcinoma										
NM	88	55	33	60.56	63.45	44.97(67.03)	14.61(5.03,58.45)	< 0.0001	-	0.7768(0.7161,0.83)
LNM	87	57	30	60.05	62.77	92.96(119.29)	34.61(10.28,152.48)	0.0603	0.6133	0.8584(0.802,0.914)
DM	42	29	13	59.13	59.23	122.87(135.63)	69.285(17.85,224.68)	< 0.0001	< 0.0001	0.9262(0.873,0.979)
Lung cancer										
NM	3098	1088	2010	60.13	62.43	11.49(26.85)	5.54(3.24,9.99)	< 0.0001	-	0.5979(0.5774, 0.6184)
LNM	2059	647	1412	60.3	62.48	15.11(36.78)	6.08(3.58,11.52)	< 0.0001	0.0002	0.6296(0.6084, 0.6509)
DM	2379	803	1576	58.89	62.16	30.52(66.10)	8.9(4.61,21.39)	< 0.0001	< 0.0001	0.7268(0.7091, 0.7446)
Liver cancer										
NM	3446	554	2892	56.82	55.36	14.13 (41.30)	4.915(3.04,8.70)	< 0.0001	-	0.5675(0.5467, 0.5883)
LNM	450	82	368	56.29	55.76	25.93(59.54)	6.535(3.55,15.63)	< 0.0001	< 0.0001	0.6537(0.6216, 0.6859)
DM	451	75	376	56.88	54.55	30.88 (69.07)	6.93(3.85,18.92)	< 0.0001	< 0.0001	0.6841(0.6533, 0.7149)
Testicular cancer										
NM	10	0	10	0.00	64.20	44.38 (119.34)	5.65(3.76,10.57)	0.2684	-	0.6377(0.4697, 0.8058)
LNM	6	0	6	0	37.67	22.68 (18.23)	22.255(12.43,23.71)	0.0065	0.1471	0.8479(0.6379, 1.0)
Cervical cancer										
NM	1889	1889	0	51.27	0	9.84 (16.05)	6.3(3.9,10.96)	< 0.0001	-	0.6403(0.6186, 0.6621)
LNM	188	188	0	50.85	0	25.32 (55.11)	9.095(5.52,19.65)	< 0.0001	< 0.0001	0.744(0.7016, 0.78)
DM	92	92	0	52.13	0	18.29 (40.10)	7.94(4.45,15.53)	< 0.0001	0.0252	0.7168(0.6628, 0.7708)

SD standard deviation,LNM lymph node metastasis, DM distant metastasis.

The ROC were constructed for NM, LNM or DM vs healthy control

	Count		Age				p value		ROC	
Laryngocarcinoma										
NM	72	4	68	60.75	64.23	7.39(6.30)	5.61(3.62,8.68)	0.0393	-	0.6079(0.5451,0.67)
LNM	286	277	64.33	62.76	63.38	7.19(8.40)	5.13(2.87,8.95)	0.0507	0.3599	0.5589(0.5199,0.59)
DM	31	0	31	0.00	64.35	10.77(9.98)	9(4.43,12.44)	0.3829	0.8207	0.6781(0.5709,0.78)
Periampullary carcinoma										
NM	56	19	37	57.21	56.84	29.03(68.28)	6.31(3.76,27.07)	0.0001	-	0.6643(0.5792, 0.7493)
LNM	8	5	3	65.20	54.00	51.41(59.82)	30.35(8.39,58.23)	0.0009	0.2341	0.871(0.7417, 1)
DM	19	7	12	52.57	62.08	101.91(136.96)	19.56 (11.37,110.625)	< 0.0001	0.0187	0.8504(0.7223, 0.9784)
Thyroid cancer										
NM	2771	2134	637	46.2	46.24	6.83(11.03)	4.78(2.94,8.01)	0.0003	-	0.5434(0.5215, 0.5653)
LNM	648	449	199	42.98	42.08	6.64 (8.95)	4.795(2.83,8.25)	0.0073	> 0.9999	0.5451(0.516, 0.57)
DM	58	42	16	50.24	46.75	8.45(11.22)	5.09(3.17,9.25)	0.194	> 0.9999	0.5711(0.4932, 0.6)
Colorectal cancer										
NM	2990	1109	1881	60.52	61.46	14.64 (34.34)	7.00(4.27,12.58)	< 0.0001	-	0.6775(0.658, 0.69)
LNM	499	206	293	59.37	59.93	32.71 (63.74)	10.9(6.03,25.46)	< 0.0001	< 0.0001	0.7917(0.7665, 0.8169)
DM	997	362	635	58.01	60.91	58.95 (94.39)	16.84(6.99,63.17)	< 0.0001	< 0.0001	0.8299(0.8117, 0.8481)
Lymphoma										
NM	27	13	14	53.85	56.43	6.014 (4.55)	4.33(2.76,7.03)	> 0.9999	-	0.5304(0.4207, 0.6401)
LNM	2	2	-	47.5	0.00	40.26(45.49)	40.255(24.17,56.33)	0.1572	0.1997	0.8957(0.7503, 1.0)
DM	4	3	1	16.00	52.67	12.76(7.41)	13.855(7.78,18.83)	0.0816	0.1607	0.8193(0.6181, 1.0)
Ovarian cancer										
NM	603	604	0	51.34	0.00	21.11(49.22)	7.56(3.83,16.36)	< 0.0001	-	0.6773(0.6488,0.70)
LNM	96	96	0	53.21	0	20.72(32.06)	9.39(6.00,19.75)	< 0.0001	0.3988	0.7852(0.7374,0.83)
DM	102	102	0	54.32	0.00	34.86(63.61)	10.95(4.93,28.99)	< 0.0001	0.053	0.7324(0.6966, 0.7682)
Bladder cancer										
NM	466	79	387	63.90	66.56	8.78(21.95)	4.7(3,7.98)	0.036	-	0.5487(0.5166,0.58)
LNM	11	1	10	64.00	70.70	32.20(84.81)	5.1(3.6,8.03)	0.245	0.7051	0.6051(0.4718,0.73)
DM	34	5	29	61.00	68.10	34.51(67.81)	9.88(5.25,20.10)	< 0.0001	< 0.0001	0.7453(0.6469,0.84)
Skin cancer										

SD standard deviation,LNM lymph node metastasis, DM distant metastasis.

The ROC were constructed for NM, LNM or DM vs healthy control

	Count			Age				p value	ROC	
NM	176	87	89	65.69	63.5	6.14 (4.60)	5.01(3.10,7.91)	0.0669	-	0.5544(0.5091, 0.5997)
LNM	14	5	9	51.00	52.89	7.12 (6.00)	5.215(3.89,7.21)	0.5778	> 0.9999	0.6021(0.4843, 0.7198)
DM	2	1	1	84.00	52.00	5.25(1.85)	5.25(4.60,5.91)	> 0.9999	> 0.9999	0.581(0.4195, 0.74)
Prostatic cancer										
NM	499	0	499	0.00	72.90	8.30 (14.17)	5.02(3.17,8.64)	< 0.0001	-	0.5677(0.5363, 0.5991)
LNM	27	0	27	0.00	72.63	7.77 (5.078)	6.77(4.06,8.8)	0.014	0.3661	0.6626(0.573, 0.75)
DM	201	0	201	0.00	73.29	11.887(31.77)	5.45(3.03,10.51)	0.0001	0.9397	0.5913(0.547, 0.63)
Breast cancer										
NM	2843	2843	0	50.73	0	8.13(8.92)	5.94(3.59,9.80)	< 0.0001	-	0.614(0.593, 0.634)
LNM	454	454	0	50.87	0.00	10.39(14.40)	6.775(4.42,11.99)	< 0.0001	< 0.0001	0.6788(0.6489, 0.7087)
DM	527	527	0	52.15	0.00	16.68(35.00)	7.87(4.44,14.32)	< 0.0001	< 0.0001	0.6979(0.6692, 0.7267)
Neuroendocrine carcinoma										
NM	24	14	10	49.36	59.30	12.25 (23.39)	7.175(3.87,9.29)	0.0099	-	0.653(0.5484, 0.75)
LNM	1	0	1	0.00	50.00	10.02()	10.02(10.02,10.02)		-	0.8682(0.8458, 0.8905)
Renal Cell Cancers										
NM	791	306	485	58.02	58.08	12.90 (37.39)	5.4(3.18,9.9)	< 0.0001	-	0.5939(0.5668, 0.6)
LNM	29	5	24	59.40	57.71	9.48 (10.26)	4.91(3.01,10.17)	0.2791	> 0.9999	0.5899(0.4721, 0.7078)
DM	82	22	60	54.27	61.25	14.39(52.16)	5.21(2.81,10.70)	0.079	> 0.9999	0.572(0.5019, 0.64)
Esophagus cancer										
NM	1034	239	795	64.01	63.7	9.561 (30.12)	4.96(3.08,8.06)	< 0.0001	-	0.5596(0.5339, 0.5854)
LNM	169	19	150	64.95	64.87	14.846(52.62)	6.01(3.35,10.71)	< 0.0001	0.0175	0.6232(0.5771, 0.6692)
DM	125	14	111	63.5	63.77	17.17 (48.23)	6.18(3.39,10.97)	0.0001	0.1068	0.6102(0.554, 0.66)
Fallopian Tube Cancer										
NM	6	6	0	67.67	0	4.91 (3.89)	3.695(3.41,5.28)	> 0.9999	-	0.5284(0.3134, 0.7435)
DM	4	4	0	53	0	10.17(4.11)	9.405(7.49,12.08)	0.0487	-	0.8257(0.7163, 0.9352)
Ureter cancer										
NM	9	8	1	53	69	28.09 (45.31)	7.66(4.47,8.5)	> 0.9999	-	0.672(0.4915, 0.85)
LNM	1	0	1	0	82	33.15()	33.15(33.15,33.15)	0.0487	0.7273	0.8705(0.69, 1.051)
DM	2	1	1	52	62	25.34(25.77)	25.34(16.23,34.45)		-	0.9989(0.9966, 1.0)

SD standard deviation,LNM lymph node metastasis, DM distant metastasis.

The ROC were constructed for NM, LNM or DM vs healthy control

	Count		Age		p value		ROC			
Craniofacial malignant tumour										
NM	262	82	180	57.79	59.17	9.95(23.29)	6.25(3.65,9.29)	< 0.0001	-	0.6204(0.5821, 0.6586)
LNM	119	28	91	56.79	59.16	10.77(10.98)	7.81(4.32,12.05)	< 0.0001	0.0244	0.5933(0.4295, 0.7571)
DM	14	1	13	77	60.17	7.35(6.19)	6.3(3.3,8.10)	0.6664	> 0.9999	0.6936(0.642, 0.74)
Vulvar cancer										
NM	35	35	59	0	0	9.15(7.11)	7.99(4.45,12.25)	0.0007	-	0.6825(0.5837, 0.7813)
LNM	10	10	53.4	0	0	3.69(1.10)	3.49(3.1,4.47)	> 0.9999	0.01	0.5855(0.499, 0.67)
DM	7	7	61.14	0	0	7.08 (4.32)	7.31(4.08,10.63)	0.824	> 0.9999	0.6196(0.3764, 0.8629)
Gastric cancer										
NM	1315	410	905	58.29	61.05	20.72 (51.68)	6.4(3.67,12.53)	< 0.0001	-	0.647(0.6242, 0.66)
LNM	460	139	321	55.78	62.45	34.65(74.86)	8.975(5.52,19.34)	< 0.0001	< 0.0001	0.7623(0.7355, 0.7891)
DM	240	86	154	54.92	61.22	55.39 (100.78)	10.40(4.33,43.78)	< 0.0001	< 0.0001	0.7359(0.6955, 0.7764)
Thymic cancer										
NM	12	3	9	45.67	60.22	6.77(6.81)	3.51(2.74,7.57)	> 0.9999	-	0.5046(0.3393, 0.6)
LNM	1	1	0	48	0	28.13()	28.13(28.13,28.13)	> 0.9999	0.9451	0.5097(0.156, 0.86)
DM	3	1	2	46	59.5	5.64 (4.74)	4.41(3.02,7.64)		-	0.9977(0.9946, 1.0)
Pancreatic cancer										
NM	335	149	186	60.28	61.21	75.64(108.64)	22.71(6.97,95.74)	< 0.0001	-	0.8247(0.7947, 0.8547)
LNM	62	18	44	64.06	59.66	79.73(116.23)	30.19(7.85,100.37)	< 0.0001	> 0.9999	0.8587(0.799, 0.91)
DM	253	93	160	58.94	60.28	122.53(131.12)	57.66(17.42,189.06)	< 0.0001	< 0.0001	0.9113(0.8863, 0.9362)
Vaginal cancer										
NM	14	14	0	52.21	0	27.57 (58.09)	8.105(5.00,11.54)	0.0055	-	0.7422(0.6302, 0.8543)
LNM	3	3	0	51.67	0	8.02(3.93)	6.08(5.76,9.31)	0.4835	> 0.9999	0.7354(0.5798, 0.8911)
DM	7	7	0	54	0	14.05 (9.51)	14.33(6.19,19.55)	0.015	> 0.9999	0.8075(0.6508, 0.9641)
Penile cancer										
NM	48	0	48	0	56.56	5.15(4.10)	4.04(2.49,7.04)	> 0.9999	-	0.5267(0.4416, 0.6118)
LNM	9	0	9	0	55.22	4.91(4.03)	3.65(2.18,7.1)	> 0.9999	> 0.9999	0.547(0.3552, 0.73)
DM	8	0	8	0	56.75	6.73(6.63)	3.91(2.80,7.61)	> 0.9999	> 0.9999	0.5056(0.295, 0.71)
Endometrial cancer										

SD standard deviation,LNM lymph node metastasis, DM distant metastasis.

The ROC were constructed for NM, LNM or DM vs healthy control

	Count		Age				p value		ROC	
NM	398	398	0	55.49	0	10.59 (16.72)	6.145(3.76,10.54)	< 0.0001	-	0.6371(0.6043, 0.6
LNM	27	27	0	57.78	0	24.65 (23.68)	15.51(10.77,32.66)	< 0.0001	< 0.0001	0.8868(0.8217, 0.9518)
DM	13	13	0	55.38	0	18.76 (20.35)	13.41(3.23,19.37)	0.0075	0.2417	0.7282(0.5379, 0.9185)
SD standard deviation,LNM lymph node metastasis, DM distant metastasis.										
The ROC were constructed for NM, LNM or DM vs healthy control										

We constructed ROC curves for the serum CA242 values of the patients with each type of tumor versus that of healthy controls. The AUC value positively correlated with metastasis in most tumors. In patients with cholangiocarcinoma with LNM or pancreatic cancer with DM, the AUC of CA242 was greater than 0.9, indicating that CA242 has a high diagnostic value. In 6 diseases including cholangiocarcinoma, gallbladder cancer, periampullary carcinoma, colorectal cancer, gastric cancer, and pancreatic cancer, when LNM or DM appeared, the AUC values were all significantly higher than 0.7, and DM produced a larger increase than LNM (Table 2).

CA242 in different clinical stages

We analyzed the serum CA242 values of 11 types of tumors in 2,500 patients who had certain clinical staging information.

We found that the mean and median levels of serum CA242 in most tumor patients increased with stage progression and were almost all higher than those in healthy controls. The median CA242 level in stage IV gastric cancer was 22.87 (7.33, 84.00), and that in stage IV colorectal cancer was 20.48 (7.74, 61.255). Both of these values were approximately five times higher than the value for the healthy controls [4.32 (2.46, 7.26)]. The means of some tumors in stage IV, including lung cancer (31.65 ± 67.96), ovarian cancer (34.37 ± 69.27) and cervical cancer (26.04 ± 47.08), were approximately 5–6 times higher than the mean of the healthy controls (5.58 ± 4.56), but the corresponding medians were only approximately two times higher. However, the medians in ovarian cancer and lung cancer did not change significantly between stages II and III. No significant differences were observed in the following diseases: nasopharyngeal carcinoma in stage I or II, laryngeal cancer in stage I or II, bladder cancer, renal cancer, esophageal cancer, and endometrial cancer (Table 3 and Fig. 3).

Table 3
CA242 in different clinical stages

	Count			Age		mean(SD)	median(25%,75%)	P value		ROC
	Case	Female	Male	Female	Male			control vs	I vs	AUC(95% confidence interval)
Colorectal cancer	2205	823	1382	59.07	60.13	28.19(45.2)	11.0725(5.66,10.95)	-	-	-
I	517	200	317	59.82	60.74	9.97(11.2)	6.95(4.68,10.95)	< 0.0001	-	0.684(0.658, 0.7099)
II	795	280	515	61.44	62.10	11.8(12.77)	8.04(4.98,13.22b)	< 0.0001	< 0.0001	0.7394(0.7171, 0.7617)
III	742	285	457	58.48	59.84	24.32(54.21)	8.82(5.24,17.54b)	< 0.0001	< 0.0001	0.7431(0.7191, 0.7671)
IV	151	58	93	56.53	57.84	66.67(102.62)	20.48(7.74,61.255b)	< 0.0001	< 0.0001	0.8612(0.8235, 0.899)
Nasopharyngeal carcinoma	215	57	158	47.40	50.84	11.1525(13.6875)	6.7725(4.285,13.9825)	-	-	-
I	3	2	1	43.00	48.00	8.56(8.67)	4.88(3.61,11.67)	> 0.9999	-	0.6065(0.08769, 1.125)
II	13	3	10	47.67	53.90	11.15(8.7)	7.89(5.74,16.02)	> 0.9999	> 0.9999	0.6028(0.3338, 0.8719)
III	91	26	65	49.27	50.42	10.91(13.63)	6.39(3.47,12.82)	< 0.0001	> 0.9999	0.6537(0.5929, 0.7145)
IV	108	26	82	49.65	51.04	13.99(23.75)	7.93(4.32,15.42)	< 0.0001	> 0.9999	0.7098(0.6529, 0.7668)
Lung cancer	2731	933	1798	60.00	61.91	17.59(40.6675)	6.4275(3.93,12.81)	-	-	-
I	1522	531	991	58.76	61.05	11.02(21.6)	6.1(3.64,10.83)	< 0.0001	-	0.6301(0.6073, 0.6528)
II	28	4	24	63.25	60.75	15.46(33.41)	4.67(3.34,9.01)	0.5444	> 0.9999	0.5808(0.4727, 0.6889)
III	57	16	41	59.63	64.29	12.23(39.7)	5.5(3.84,8.56)	0.1466	> 0.9999	0.6009(0.5284, 0.6733)
IV	1124	382	742	58.36	61.53	31.65(67.96)	9.44(4.9,22.84)	< 0.0001	< 0.0001	0.8101(0.7941, 0.8262)
Cervical cancer	999	999	0	50.57	0.00	14.8775(25.36)	6.9275(4.645,13.7825)	-	-	-
I	519	519	0	48.70	0	10.06(21.11)	6.32(4.09,10.76)	< 0.0001	-	0.652(0.6226, 0.6813)
II	434	434	0	52.58	0	11.37(15.01)	7.4(4.44,12.63)	< 0.0001	0.0762	0.6875(0.6569, 0.7182)
III	31	31	0	52.74	0	12.04(18.24)	5.88(3.93,10.86)	0.0606	> 0.9999	0.6215(0.5142, 0.7289)
IV	15	15	0	48.27	0	26.04(47.08)	8.11(6.12,20.88)	< 0.0001	0.0431	0.8324(0.7498, 0.9149)
Laryngocarcinoma	268	9	259	59.77	63.39	7.0975(6.435)	5.0025(3.0275,9.0025)	-	-	-
I	131	3	128	58.33	61.24	6.12(4.61)	5.01(2.7,8.04)	0.3158	-	0.5475(0.4938, 0.6012)
II	55	4	51	66.75	63.73	5.74(4.4)	4.05(2.37,8.63)	> 0.9999	> 0.9999	0.5038(0.4182, 0.5894)
III	44	1	43	40.00	64.84	6.12(4.23)	5.06(2.9,9.15)	> 0.9999	> 0.9999	0.5468(0.4536, 0.64)
IV	38	1	37	74.00	63.76	10.41(12.5)	5.89(4.14,10.19)	0.0168	0.6204	0.638(0.5503, 0.7256)
Ovarian cancer	624	624	0	51.26	0.00	19.525(31.8825)	8.955(5.1675,18.6225)	-	-	-

SD standard deviation

The ROC were constructed for stage I, stage II, stage III or stage IV vs healthy control

	Count		Age				P value		ROC	
I	127	127	0	48.08	0	11.55(10.95)	7.62(4.87,15.39)	< 0.0001	-	0.7377(0.6933, 0.7821)
II	78	78	0	51.50	0	13.15(12.35)	8.5(5.92,14.05)	< 0.0001	> 0.9999	0.7676(0.7151, 0.8201)
III	334	334	0	53.42	0	19.03(34.96)	8.73(4.91,16.74)	< 0.0001	> 0.9999	0.7326(0.7001, 0.7652)
IV	85	85	0	52.04	0	34.37(69.27)	10.97(4.97,28.31)	< 0.0001	0.414	0.7709(0.7134, 0.8284)
Bladder cancer	66	10	56	44.04	69.26	12.1525(16.62)	6.02(3.5475,10.9575)	-	-	-
I	20	2	18	48.50	65.72	5.23(4.37)	4.1(3.6,4.67)	> 0.9999	-	0.502(0.4086, 0.5953)
II	14	0	14	0	70.80	7.32(5.44)	5.62(3.84,8.26)	0.1614	0.7376	0.6547(0.5372, 0.7721)
III	11	2	9	72.67	70.38	5.78(4.3)	5(2.72,7.51)	> 0.9999	> 0.9999	0.5275(0.3561, 0.6989)
IV	21	6	15	55.00	70.13	30.28(52.37)	9.36(4.03,23.39)	0.006	0.0955	0.7015(0.5636, 0.8393)
Renal carcinoma	95	31	64	58.76	57.57	15.205(23.9775)	4.9275(3.3875,13.455)	-	-	-
I	46	13	33	60.33	55.09	6.4(4.1)	5.65(3.5,8.75)	0.269	-	0.5806(0.4967, 0.6646)
II	10	5	5	56.60	61.71	5.98(6.33)	3.04(1.79,8.35)	> 0.9999	> 0.9999	0.5659(0.3485, 0.7832)
III	17	5	12	64.60	55.33	9.2(7.84)	5.43(4.15,14.99)	0.3551	> 0.9999	0.6199(0.4626, 0.7772)
IV	22	8	14	53.50	58.14	39.24(77.64)	5.59(4.11,21.73)	0.014	0.8486	0.6818(0.5704, 0.7932)
Esophagus cancer	547	92	455	63.46	62.13	9.7475(19.805)	5.2525(3.435,8.4225)	-	-	-
I	99	26	73	63.46	63.05	5.78(3.36)	5.2(3.45,7.12)	0.1949	-	0.5624(0.5103, 0.6144)
II	241	42	199	61.42	62.96	6.77(6.32)	5.12(3.11,7.85)	0.0094	> 0.9999	0.5643(0.5249, 0.6037)
III	187	21	166	62.29	63.04	16.38(54.94)	5.48(3.34,10.56)	< 0.0001	> 0.9999	0.6105(0.5655, 0.6555)
IV	20	3	17	66.67	59.47	10.06(14.6)	5.21(3.84,8.16)	0.6519	> 0.9999	0.5892(0.4611, 0.7174)
Gastric cancer	1031	316	715	55.74	60.52	30.6025(48.2)	11.2075(5.15,10.815)	-	-	-
I	242	65	177	58.23	59.83	7.92(6.33)	6.25(3.76,9.98)	< 0.0001	-	0.6295(0.5901, 0.669)
II	191	67	124	53.82	60.68	11.27(14.55)	6.97(4.48,11.65)	< 0.0001	0.4399	0.6801(0.6391, 0.7211)
III	496	139	357	56.01	61.06	33.25(71.93)	8.74(5.03,20.64b)	< 0.0001	< 0.0001	0.7489(0.722, 0.7758)
IV	102	45	57	54.89	60.51	69.97(99.99)	22.87(7.33,84.00b)	< 0.0001	< 0.0001	0.8508(0.8073, 0.8942)
Endometrial cancer	104	104	0	56	0	11.8275(9.5425)	9.3(6.2725,14.5)	-	-	-
I	85	85	0	56.57	0	8.12(6.85)	5.67(3.73,10.19)	0.0008	-	0.6228(0.5594, 0.6863)
II	4	4	0	59.50	0	17.53(14.04)	13.21(8.27,22.46)	0.0402	0.3852	0.8703(0.7426, 0.998)
III	13	13	0	57.77	0	13.8(11.31)	10.46(7.34,15.38)	0.0028	0.2008	0.7705(0.6031, 0.9378)

SD standard deviation

The ROC were constructed for stage I, stage II, stage III or stage IV vs healthy control

	Count		Age		P value		ROC				
	Case	Female	Male	Female	Male	Mean(SD)	Median(25%,75%)	vs. Liver	vs. Bone	vs. Brain	vs. Multiple
IV	2	2	0	49.50	0	7.86(5.97)	7.86(5.75,9.97)	> 0.9999	> 0.9999	0.6679(0.321, 1.015)	
SD standard deviation											
The ROC were constructed for stage I, stage II, stage III or stage IV vs healthy control											

Then, the ROC of the CA242 level in each tumor stage relative to that in the healthy controls was calculated. The analysis showed that the AUC of CA242 gradually increased with progression in most tumors. Among these tumors, colorectal cancer, gastric cancer, cervical cancer, and lung cancer were particularly remarkable. Especially in stage IV, the AUC values of these four tumors were greater than 0.8, specifically 0.8612 (0.8235, 0.899) for colorectal cancer, 0.8508 (0.8073 0.8942) for gastric cancer, 0.8324 (0.7498, 0.9149) for cervical cancer, and 0.8101 (0.7941, 0.8262) for lung cancer, showing that CA242 was valuable in predicting stage IV disease for these four tumors (Table 3 and Fig. 3).

CA242 in different metastatic sites

Based on the above results, we noticed that serum CA242 levels exhibited a significant change with DM and had the capacity to predict metastasis in some tumors. Therefore, we wanted to study whether there is a correlation between patient serum CA242 levels and sites of metastasis. Therefore, we divided 3,953 patients with one of five cancers who had defined metastatic site information into group NM and group DM.

We found that the mean and median values of the serum CA242 level in DM patients in most diseases were higher than those in NM patients and healthy controls, but there were no significant differences among the patients with different metastatic sites within each tumor type (Supplemental Table 3). We speculated that this lack of difference was due to the small sample sizes for some metastatic sites and the large variation range of CA242. Therefore, we calculated the median fold change in DM patients relative to NM patients for every tumor type and the log₂ (fold change) value of the serum CA242 level for each metastatic site and found the following results: multiple metastases: 1.228 (-0.1189, 3.079), liver metastasis: 1.071 (-0.1195, 3.059), bone metastasis: 0.7286 (-0.2386, 1.979), brain metastasis: 0.6536 (0.2648, 2.401), and lung metastasis: 0.4921 (-0.3371, 1.676). There were significant differences among the metastatic sites other than the brain (Table 4).

Table 4
CA242 in different metastatic sites

	Count		Age		P value						
	Case	Female	Male	Female	Male	Mean(SD)	Median(25%,75%)	vs. Liver	vs. Bone	vs. Brain	vs. Multiple
Lung	362	112	250	56.67	56.69	0.8567(1.889)	0.4921(-0.3371,1.676)	0.0003	> 0.9999	> 0.9999	< 0.0001
Liver	557	167	390	58.93	61.44	1.437(2.121)	1.071(-0.1195,3.059)	-	0.0114	> 0.9999	> 0.9999
Bone	719	244	475	57.61	61.47	1.027(1.837)	0.7286(-0.2386,1.979)	-	-	> 0.9999	0.0006
Brain	58	23	35	56.91	63.20	1.244(1.661)	0.6536(0.2648,2.401)	-	-	-	> 0.9999
Multiple	604	228	376	57.75	60.81	1.509(2.167)	1.228(-0.1189,3.079)	-	-	-	-
SD standard deviation											

Discussion

Although CA242 has been identified and used in clinical practice for some time, this is the first study to profile the levels of this biomarker in 35 different tumors in a large number of patients. Among the 35 tumor types, the serum CA242 level changes in 23 tumor types had never been reported before. We also found that serum CA242 levels in patients with metastatic tumors might be related to the target organs containing metastases for the first time.

We found that CA242 levels were elevated in a variety of digestive system cancers, including pancreatic cancer, gallbladder cancer, cholangiocarcinoma, colorectal cancer, and gastric cancer, which was consistent with previous reports. The AUC values of the ROC curves for pancreatic cancer, gallbladder carcinoma, and cholangiocarcinoma were all greater than 0.8, but only pancreatic cancer has been studied in detail[4, 10, 13, 17, 22, 25–27]. Previous studies have shown that CA242 alone or in combination with other biomarkers can predict the diagnosis, progression, and prognosis of pancreatic cancer[4, 7, 10, 12–16, 23, 24]. Pancreatic cancer has been the leading clinical application for CA242 because of its excellent performance in this cancer. Some small-scale studies have investigated CA242 in gallbladder carcinoma and cholangiocarcinoma[7, 14, 25, 28], but due to the sample size or quality of these studies, the credible AUC values for these two carcinomas are still unknown. Therefore, our findings indicate that CA242 is also suitable for use as a biomarker for cholangiocarcinoma and gallbladder cancer, whose AUCs were 0.8145 (0.7737, 0.8553) and 0.8349 (0.8157, 0.8542), respectively (Table 1).

The study of serum CA242 levels in the ampulla of Vater carcinomas, including ampullary carcinoma and duodenal papilla carcinoma, is shown for the first time. A previous study reported that the mean level in the ampulla of Vater carcinoma is 21.1 ± 26.1 [29], but the level was 47.87 ± 93.24 for the ampulla of Vater carcinoma in our research. Furthermore, the median level was 2.70 times that of healthy controls, and the AUC value reached 0.7268 (0.6581, 0.7955) (Table 1). The discrepancies between the previous study and our study may be due to the sample size in the other study being too small to produce a statistical error or the difference between the ampulla of Vater carcinoma and duodenal papilla carcinoma not being negligible.

CA242 has been reported to be more sensitive and specific than CA50 and CEA in Dukes' A-D colorectal cancer[22], in addition to its considerable value in predicting recurrence and metastasis in clinical stage II and III colorectal cancer[18]. Moreover, many studies have demonstrated that CA242 works well in predicting the diagnosis, progression, and prognosis of colorectal cancer in combination with other tumor markers[18, 19, 26, 30]. Our results showed that the mean value in colorectal cancer was 26.50 ± 59.58 and that the AUC was 0.7241 (0.7073, 0.7408) (Table 1), which was consistent with previous studies[22, 26, 27].

CA242 levels in patients with gastric cancer differed between stage IV and non-stage IV[20], but alone, CA242 was not a good predictor of LNM[21]. However, in a study by Fangxuan Li et al.[31], the mean value of 29.84 ± 83.54 in gastric cancer was not much different from our data, but their AUC for gastric cancer relative to healthy people was 0.809, which is much higher than the value of 0.6839 (0.604, 0.8202) found in this study (Table 1). We suggest that a possible explanation may be that their sample size is too small and that their mean lower than the control is 3.85 ± 3.13 . A surprising finding was that the CA242 level in patients with gastric cardia adenocarcinoma was not significantly different from that in gastric cancer patients.

In this study, the mean value in lung cancer was 18.49 ± 45.97 (Table 1), but Huaiqian Dou et al.[10] reported that the mean in lung cancer was 9.34 ± 13.67 . In contrast, Xiaochuan Wang et al. [32] reported that it was 28.39 ± 51.91 . These differences might be caused by a sampling error, detection kit choice, and instrument differences. However, the results we reported have the largest sample size and therefore higher credibility. The mean value in ovarian cancer was 19.52 ± 42.27 (Table 1), which was slightly higher than the previously reported value of 11.40 ± 16.88 [10], and the mean in cervical cancer was 11.54 ± 23.97 , which was very similar to the previously reported value[10]. The levels in nasopharyngeal carcinoma, craniofacial malignant tumor, endometrial cancer, breast cancer, renal cell cancer, liver cancer, esophageal cancer, and prostate cancer patients were significantly higher than those in healthy controls (Table 1), indicating that CA242 has potential clinical value in these diseases. Although mediastinal cancer, testicular cancer, ureteral cancer, and neuroendocrine cancer patients had higher mean and median values than health controls (Table 1), the sample size was too small to identify significant differences.

The CA242 levels in colorectal cancer and gastric cancer patients increased not only with the appearance of LNM or DM but also with advancement from stage I to IV[18, 20–22, 26, 30]. The results mentioned above are consistent with the trends in a previous study, and we also found that CA242 was able to distinguish colorectal cancer and gastric cancer patients from healthy controls (Table 1). The AUC values for diagnosing stage IV disease reached 0.85 or higher and, for DM, reached 0.8299 (0.8117, 0.8481) and 0.7359 (0.6955, 0.7764) in colorectal and gastric cancer patients, respectively (Table 2 and Table 3). In patients with pancreatic cancer, cholangiocarcinoma, gallbladder carcinoma, lung cancer, cervical cancer, ovarian cancer, periampullary carcinoma, bladder cancer, breast cancer, or endometrial cancer, serum CA242 levels were positively correlated with LNM and DM (Table 2). Some diseases, such as pancreatic cancer, have been reported, but the rest are reported here for the first time. There were no significant differences in CA242 levels between patients with laryngocarcinoma, esophageal cancer, nasopharyngeal cancer, or renal cancer metastasis and those with NM nor were there different among patients with various stages of disease for these cancers (Table 2).

Among thyroid cancer, prostate cancer, and craniofacial malignant tumor patients, the level of CA242 increased with metastasis, but the differences were not significant (Table 2). While endometrial cancer and bladder cancer showed significant decreases in the sample, although the CA242 level showed an increasing trend with advancing clinical stage, the data showed no significant differences (Table 3). The remaining tumor sample sizes were too small to draw valid conclusions. According to whether the CA242 level increased with metastasis or stage advancement in the tumors listed in Tables 2 and 3, we identified tumors as "CA242 progression-positive tumors". In these tumors, the combination of other tumor markers and CA242 could be further studied to improve the accuracy of the prediction of tumor progression. We speculate that some commonalities exist among these tumors, such as mutations in similar tumor driver genes[33], similar embryonic developmental origins, and microenvironments. Further research is needed to confirm these findings, which may have the potential to facilitate the diagnosis and treatment of tumors.

Furthermore, we also found that in all of the cancers listed in Table 4, the increase in the serum CA242 value for multiple metastases compared to NM was the largest, followed by the increases for liver metastasis and bone metastasis. Some studies have shown that the prognosis of gastric cancer with liver and bone metastasis is worse than that of any other subtype of gastric cancer, and the two organs even account for most metastatic sites [34, 35]. Interestingly, we find that similar situation also exist in colorectal cancer, lung cancer, pancreatic cancer, breast cancer and other tumors [36–40]. We deem that the liver and bones may have microenvironments conducive to the synthesis and release of CA242 molecules in the five "CA242 progression-positive tumors" or that the liver and bones enhance metastatic tumor cell growth so that more tumor cells produce more CA242, resulting in elevated levels. Therefore, CA242 may be valuable in predicting the progression of "CA242 progression-positive tumors". Moreover, studying the molecular mechanisms underlying the elevated CA242 levels may produce an understanding of the mechanisms of tumor metastasis.

However, not all malignant tumor patients' serum CA242 levels were greater than those of healthy controls. For example, the sample sizes for leukemia, laryngocarcinoma, skin cancer, and penile cancer were not small, but there were no significant differences between these patients and the healthy controls in regard to the median levels (Table 1). This finding indicated that serum CA242 levels are not suitable for diagnosing all diseases, but CA242 may be used to identify nonprimary tumors at the same site, that is, metastatic tumors with increased CA242 expression. Moreover, the median serum CA242 values of the two precancerous lesions in this study, benign colorectal neoplasms and cervical intraepithelial neoplasia, were similar to the median value of the healthy controls, and there were no significant differences. However, the median CA242 level in benign colorectal neoplasms was less than half of that in colorectal cancer, but the difference was not significant, which is probably caused by the small sample size for benign colorectal neoplasms. By increasing the number of samples, we might find a difference between these two precancerous lesions and a new marker to identify benign colorectal neoplasms and colorectal cancer, as is done for cervical cancer and cervical intraepithelial neoplasia.

This study has several limitations. First, the sample size is relatively insufficient. Although the total sample size was more than 35,000, there were 35 different kinds of diseases, so each disease included only 1,000 patients on average. Thus, some tumors, such as colorectal cancer and liver cancer, were numerous, with more than 4,000 cases. However, some had many fewer cases, such as mediastinal tumor, ureteral cancer and fallopian tube cancer, which had only 10

cases. The reasons for this situation are not only the disparity in the incidence rates of different diseases but also the previous understanding of the diagnostic role of CA242. CA242 is considered to be a diagnostic marker for digestive system tumors[10, 13, 22, 26], especially pancreatic cancer, so measuring CA242 levels is not an appropriate choice when a doctor suspects a patient may develop other tumors. Second, in the analysis of individual diseases, the subpopulations are not sufficiently accurate. In this study, we stratified subpopulations according to the metastatic status, clinical stage, and metastatic site of the tumors. Although some differences and factors that may affect the level of CA242 were revealed, we still did not find an excellent stratified method that could make the distribution concentrated and failed to find further accurate factors that influenced CA242 levels. Third, the collection of patient clinical information is relatively incomplete, and only some patients had accurate metastasis and clinical staging information. However, we gathered no staging classification information for some tumor patients, such as those with pancreatic cancer, cholangiocarcinoma or gallbladder cancer. Therefore, we missed the opportunity for further analysis of the diseases that most commonly use CA242 in the clinic. Fourth, this was a single-center, retrospective study. Therefore, the numbers of patients in each stage and metastatic status were very different, which may lead to biased conclusions. In addition, the CA242 values for different stages and metastatic states belonged to different patients. In other words, this study had neither a paired design nor a longitudinal design so some confounding factors may have influenced the conclusion of the study.

In this study, we analyzed serum CA242 levels in 35 types of neoplastic disease patients and healthy controls and found that these levels remained unchanged in benign tumors and increased most in malignant tumors, especially pancreatic cancer, gallbladder cancer, cholangiocarcinoma, and periampullary carcinoma. The CA242 levels of these malignant digestive system tumors were significantly higher than those of other tumors and were valuable for patient diagnosis. Moreover, the level of CA242 was also related to metastasis and clinical stage and was able to predict the progression of some tumors.

Conclusions

In conclusion, CA242 can not only serve as a diagnostic biomarker for malignant digestive system tumors, such as pancreatic cancer, but also predict the progression, stage, metastasis, survival, prognosis, etc. of tumors or play a role in tumors that have not received clinical attention and are awaiting further research.

Abbreviations

AJCC
American Joint Commission on Cancer
AUC
Area under the curve
DM
Distant metastasis
LNM
Lymph node metastasis
NM
No metastasis
ROC
Receiver operating characteristic

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of the Army Medical University, PLA (the approval number is KY201912), and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are 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

ZC and KS provided the concept, HW collected the data. XQ, XS, YY and HD analysed the data. YJ and JB proofread the data and results. KS and XQ drafted the manuscript and all the authors read and approved the final manuscript.

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44. **Recurrence after Resection for Ductal Adenocarcinoma of the Pancreas.**

Figures

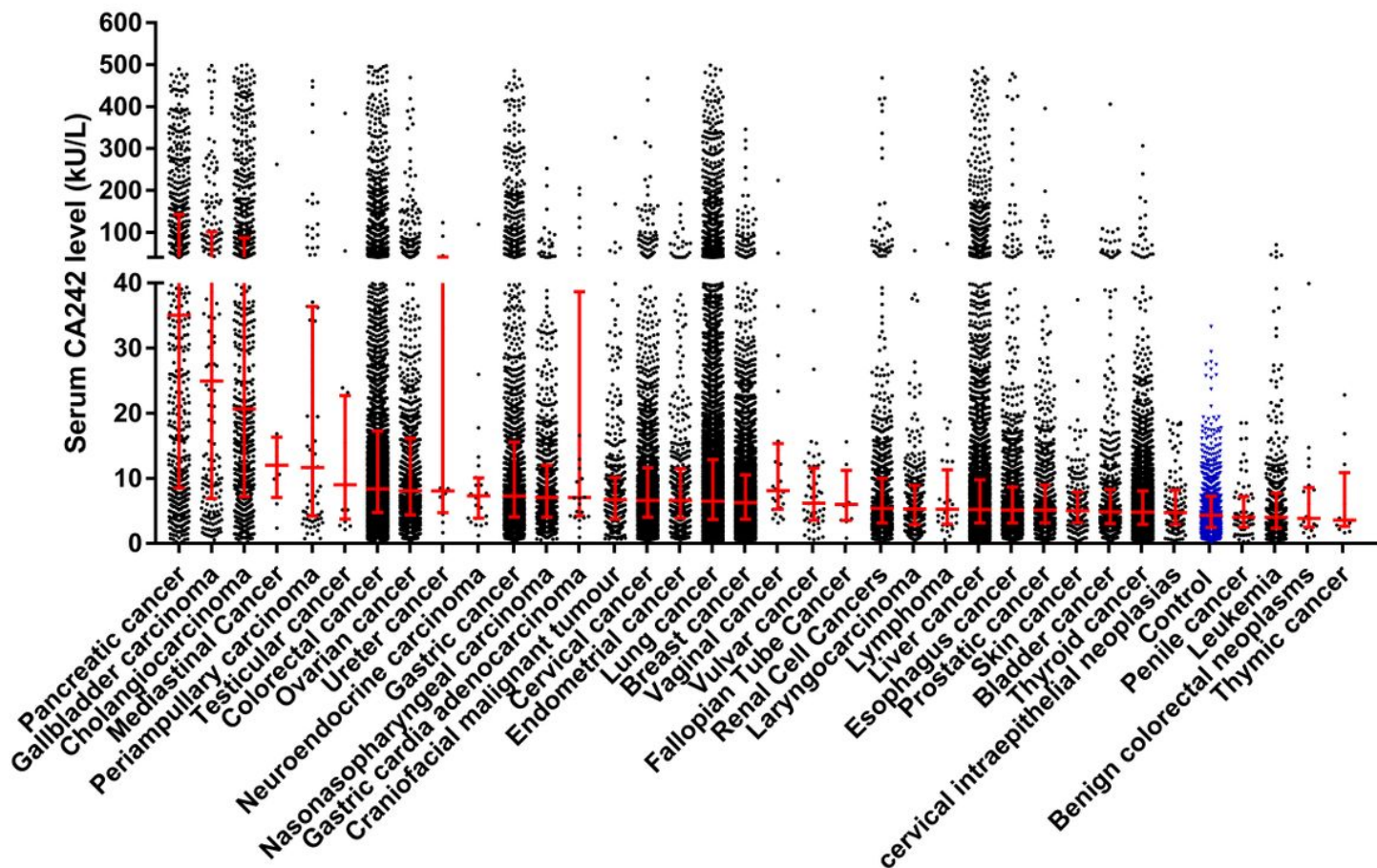


Figure 1

Serum CA242 levels in 35 different types of neoplastic diseases. The data were sorted in a descending order of the median values. CA242 levels for each group with lower quartile (25%), median (50%), and upper quartile (75%) ranges were marked in red.

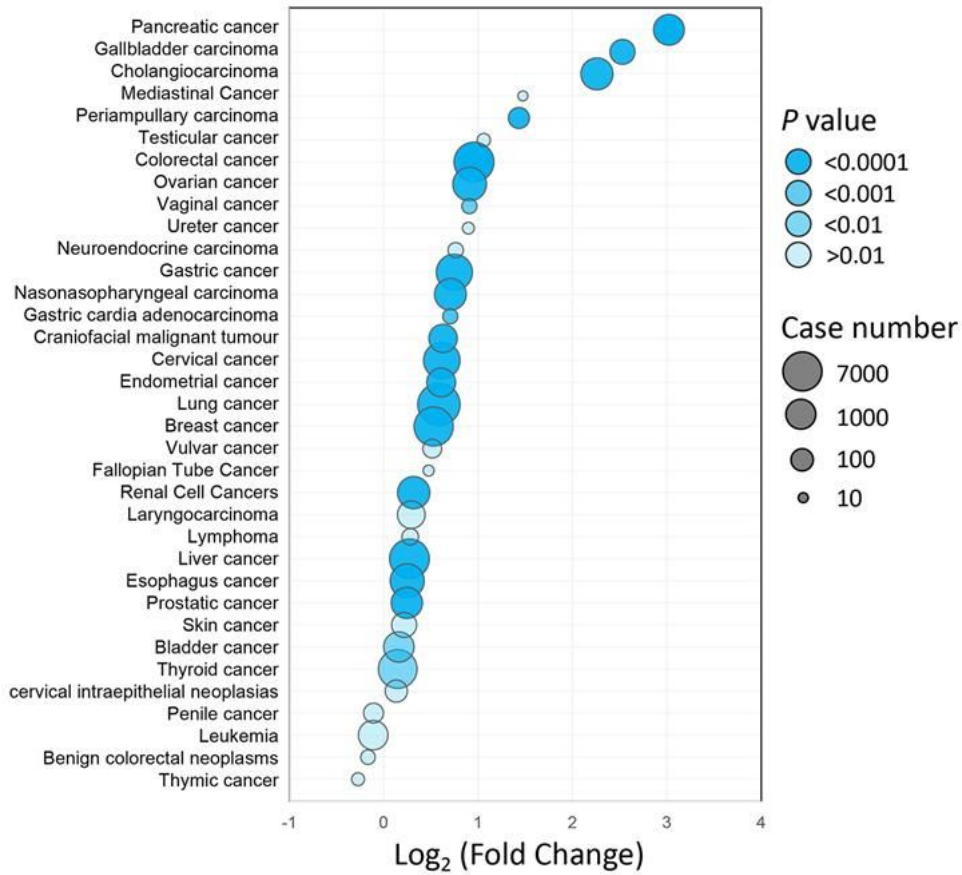


Figure 2

The relative change of serum CA242 in 35 types neoplastic disease to healthy control. Each tumor was rank in the figure according to the fold change compared with healthy control. The size of bubble was positively correlated with the case number, and the color depth was negatively correlated with the p value

Supplementary Files

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