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

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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.
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.
| Characteristics and serum CA242 levels of patients and healthy controls | Case   | Female | Male  | Female | Male  | p value | Mean(SD) | Medin(25%,75%) | P value | Fold change | Al   |
|-------------------------------------------------------------------------|--------|--------|-------|--------|-------|---------|----------|---------------|---------|-------------|------|
| 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)   | < 0.0001 | 8.12037037 | 0.6  |
| Pancreatic cancer                                                       | 650    | 260    | 390   | 60.06  | 60.65 | 0.52500 | 94.28(120.5)  | 35.08(8.51,142.23) | < 0.0001 | 5.773148148 | 0.6  |
| Gallbladder carcinoma                                                  | 193    | 125    | 68    | 60.18  | 60.90 | 0.67000 | 78.64(113.5)  | 24.94(6.94,98.67) | < 0.0001 | 4.787037037 | 0.6  |
| Cholangiocarcinoma                                                    | 856    | 355    | 501   | 62.46  | 62.70 | 0.77600 | 77.22(117.85) | 20.68(7.18,85.93) | < 0.0001 | -           | -    |
| 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 | 0.6  |
| Mediastinal Cancer                                                    | 8      | 0      | 8     | 0.00   | 55.80 | -       | 41.97(88.92)  | 12.8(9.5,15.34)   | 0.0777 | 2.777777778 | 0.6  |
| Periampullary cancer                                                  | 83     | 31     | 52    | 57.45  | 57.88 | 0.87500 | 47.87(93.24)  | 11.66(21.36,35)   | < 0.0001 | 2.699074074 | 0.6  |
| Testicular cancer                                                     | 16     | 0      | 16    | 0.00   | 52.60 | -       | 36.24(93.67)  | 9.01(4.69,21.81)  | 0.0772 | 2.085648148 | 0.6  |
| Ovarian cancer                                                        | 1211   | 1211   | 0     | 51.17  | 0.00  | -       | 19.52(42.27)  | 8.12(4.4,16.13)   | < 0.0001 | 1.89762963 | 0.6  |
| Vaginal cancer                                                        | 24     | 24     | 0     | 52.67  | 0.00  | -       | 21.19(44.67)  | 8.11(5.38,14.67)  | 0.0012 | 1.876157407 | 0.6  |
| Ureter cancer                                                         | 12     | 12     | 0     | 61.80  | 0.00  | -       | 28.59(42.75)  | 8.05(4.74,26.99)  | 0.1396 | 1.862268519 | 0.6  |
| Neuroendocrine cancer                                                 | 25     | 14     | 11    | 49.36  | 58.45 | 0.06000 | 12.16(22.90)  | 7.33(3.87,10.02)  | 0.4501 | 1.696759259 | 0.6  |
| 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 | 0.6  |
| Nasopharyngeal cancer                                                 | 51     | 6      | 31    | 48.10  | 51.46 | 0.00900 | 11.05(16.97)  | 7.05(4.02,12)    | < 0.0001 | 1.631944444 | 0.6  |
| 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 | 0.6  |
| 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 | 0.6  |
| Cervical cancer                                                       | 2169   | 2169   | 0     | 51.29  | 0.00  | -       | 11.54(23.97)  | 6.62(4.02,11.58)  | < 0.0001 | 1.532407407 | 0.6  |
| Endometrial cancer                                                   | 438    | 438    | 0     | 55.63  | 0.00  | -       | 11.70(17.66)  | 6.59(3.95,11.47)  | < 0.0001 | 1.525462963 | 0.6  |
| 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       | 0.6  |
| Breast cancer                                                         | 3824   | 3824   | 0     | 50.94  | 0.00  | -       | 9.57(16.15)   | 6.24(3.72,10.51)  | < 0.0001 | 1.443287037 | 0.6  |
| Vulvar cancer                                                         | 52     | 52     | 0     | 53.05  | 0.00  | -       | 7.82(6.38)    | 6.17(3.69,11.19)  | 0.2174 | 1.428240741 | 0.6  |
| Fallopian Tube Cancer                                                 | 10     | 10     | 0     | 61.80  | 0.00  | -       | 7.01(4.62)    | 6.01(3.65,10.15)  | > 0.9999 | 1.391203704 | 0.6  |
| 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 | 0.6  |
| Laryngocarcinoma                                                      | 333    | 24     | 309   | 58.75  | 62.48 | 0.08300 | 6.79(6.35)    | 5.29(2.91,8.85)   | 0.1694 | 1.224537037 | 0.6  |
| Lymphoma                                                              | 33     | 16     | 17    | 50.69  | 55.76 | 0.37300 | 8.91(12.53)   | 5.25(3.12,10.09)  | > 0.9999 | 1.215277778 | 0.6  |

SD standard deviation
### CA242 levels 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: 19.56 (11.37, 110.625), and DM: 39.25 (12.24, 120.94)]; 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).
| Source                  | Case | Female | Male | Female | Male | median(SD) | Median(25%,75%) | Control vs | NM vs. LNM | ROC               |
|------------------------|------|--------|------|--------|------|------------|----------------|------------|------------|-------------------|
| **Serum CA242 in different metastatic situations** | | | | | | | | | | | |
| Nasopharyngeal carcinoma | | | | | | | | | | | |
| NM                     | 323  | 95     | 228  | 49.98  | 52.25| 10.94(19.18)| 6.81(3.76,11.66)| < 0.0001 | < 0.0001 | 0.556 | 0.624(0.6387, 0.7261) |
| LNM                    | 323  | 92     | 231  | 48.86  | 50.30| 11.12(12.67)| 7.12(4.10,13.85)| < 0.0001 | 0.556 | 0.6809(0.6466, 0.7152) |
| 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(0.7161,0.82) |
| 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(0.873,0.97) |
| 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(0.608,0.6509) |
| 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.
| Cancer Type                  | Count | Age   | p value | ROC             |
|-----------------------------|-------|-------|---------|-----------------|
| **Laryngocarcinoma**        |       |       |         |                 |
| NM                          | 72    | 4     | 68      | 60.75           | 5.61(3.62,8.68) | 0.0393 - | 0.6079(0.5451,0.61) |
| LNM                         | 286   | 277   | 64.33   | 62.76           | 7.19(8.40)      | 5.13(2.87,8.95) | 0.0507 0.3599 0.5589(0.5199,0.58) |
| DM                          | 31    | 0     | 31      | 0.00            | 64.35           | 10.77(9.98)    | 9(4.43,12.44) | 0.3829 0.8207 0.6781(0.5709,0.74) |
| **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(0.5215,0.5663) |
| 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(0.6488,0.71) |
| LNM                         | 96    | 96    | 0       | 53.21           | 0              | 20.72(32.06) | 9.39(6.00,19.75) | < 0.0001 0.3988 0.7852(0.7374,0.82) |
| 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(3.7,9.8) | 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(0.4718,0.72) |
| 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          |
|------------------|-------|----------|----------|--------------|
| **Prostatic cancer** |       |          |          |              |
| NM               | 176   | 87       | 89       | 65.69        | 0.0669 - | 0.5544(0.5091, 0.5997) |
| LNM              | 14    | 5        | 9        | 51.00        | 0.5778 > | 0.9999 > | 0.6021(0.4843, 0.7198) |
| DM               | 2     | 1        | 1        | 84.00        | > 0.9999 > | 0.9999 > | 0.581(0.4195, 0.74)     |
| **Breast cancer** |       |          |          |              |
| NM               | 499   | 0        | 499      | 0.00         | < 0.0001 - | 0.5677(0.5363, 0.5991) |
| LNM              | 27    | 0        | 27       | 0.00         | 0.014 0.3661 | 0.6626(0.573, 0.75)     |
| DM               | 201   | 0        | 201      | 0.00         | 0.0001 0.9397 | 0.5913(0.547, 0.63)     |
| **Neuroendocrine carcinoma** | |          |          |              |
| NM               | 2843  | 2843     | 0        | 50.73        | 0.0099 - | 0.653(0.5484, 0.75)     |
| LNM              | 454   | 454      | 0        | 50.87        | < 0.0001 < | 0.6788(0.6489, 0.7087) |
| DM               | 527   | 527      | 0        | 52.15        | < 0.0001 < | 0.6979(0.6692, 0.7267) |
| **Renal Cell Cancers** | |          |          |              |
| NM               | 791   | 306      | 485      | 58.02        | 5.4(3.18,9.9) | < 0.0001 - | 0.5939(0.5668, 0.6)    |
| LNM              | 29    | 5        | 24       | 59.40        | 4.91(3.01,10.17) | 0.2791 > | 0.9999 > | 0.5899(0.4721, 0.7078) |
| DM               | 82    | 22       | 60       | 54.27        | 5.21(2.81,10.70) | 0.079 > | 0.9999 > | 0.572(0.5019, 0.64)    |
| **Esophagus cancer** | |          |          |              |
| NM               | 1034  | 239      | 795      | 64.01        | 4.96(3.08,8.06) | < 0.0001 - | 0.5596(0.5339, 0.5854) |
| LNM              | 169   | 19       | 150      | 64.95        | 6.01(3.35,10.71) | < 0.0001 < | 0.0175 0.6232(0.5771, 0.6692) |
| DM               | 125   | 14       | 111      | 63.5         | 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        | 4.91(3.89) | 3.695(3.41,5.28) | > 0.9999 - | 0.5284(0.3134, 0.7435) |
| DM               | 4     | 4        | 0        | 53           | 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           | 28.09(45.31) | 7.66(4.47,8.5) | > 0.9999 - | 0.672(0.4915, 0.85)    |
| LNM              | 1     | 0        | 1        | 82           | 33.15(33.15,33.15) | 0.0487 0.7273 | 0.8705(0.69, 1.051)    |
| DM               | 2     | 1        | 1        | 52           | 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.
| Craniofacial malignant tumour | Count | Age | p value | ROC |
|-------------------------------|-------|-----|---------|-----|
| NM                            | 262   | 82  | 0.0001  | 0.6204(0.5821, 0.6586) |
| LNM                           | 119   | 28  | 0.0244  | 0.5933(0.4295, 0.7571) |
| DM                            | 14    | 1   | 0.6664  | 0.6936(0.642, 0.74) |

| Vulvar cancer | Count | Age | p value | ROC |
|---------------|-------|-----|---------|-----|
| NM            | 35    | 59  | 0.0007  | 0.6825(0.5837, 0.7813) |
| LNM           | 10    | 53.4| > 0.9999| 0.5855(0.499, 0.67) |
| DM            | 7     | 61.14| 0.824  | > 0.9999 |

| Gastric cancer | Count | Age | p value | ROC |
|---------------|-------|-----|---------|-----|
| NM            | 1315  | 905 | < 0.0001| 0.647(0.6242, 0.66) |
| LNM           | 460   | 321 | < 0.0001| 0.7623(0.7355, 0.7891) |
| DM            | 240   | 154 | < 0.0001| 0.7359(0.6955, 0.7764) |

| Thymic cancer | Count | Age | p value | ROC |
|---------------|-------|-----|---------|-----|
| NM            | 12    | 45.67| > 0.9999| - |
| LNM           | 1     | 48   | > 0.9999| 0.9451 |
| DM            | 3     | 46   | > 0.9999| 0.9977(0.9946, 1.0) |

| Pancreatic cancer | Count | Age | p value | ROC |
|-------------------|-------|-----|---------|-----|
| NM                | 335   | 60.28| < 0.0001| 0.8247(0.7947, 0.8547) |
| LNM               | 62    | 64.06| < 0.0001| 0.8587(0.799, 0.91) |
| DM                | 253   | 58.94| < 0.0001| 0.9113(0.8863, 0.9362) |

| Vaginal cancer | Count | Age | p value | ROC |
|---------------|-------|-----|---------|-----|
| NM            | 14    | 52.21| 0.0055  | 0.7422(0.6302, 0.8543) |
| LNM           | 3     | 51.67| 0.4835  | > 0.9999 |
| DM            | 7     | 54   | > 0.9999| 0.8075(0.6508, 0.9641) |

| Penile cancer  | Count | Age | p value | ROC |
|----------------|-------|-----|---------|-----|
| NM             | 48    | 56.56| > 0.9999| 0.5267(0.4416, 0.6118) |
| LNM            | 9     | 55.22| > 0.9999| 0.547(0.3552, 0.73) |
| DM             | 8     | 56.75| > 0.9999| 0.5056(0.295, 0.71) |

| Endometrial cancer | Count | Age | p value | ROC |
|-------------------|-------|-----|---------|-----|
| NM                | 285   | 57.79| < 0.0001| 0.6204(0.5821, 0.6586) |
| LNM               | 119   | 56.79| 0.0244  | 0.5933(0.4295, 0.7571) |
| DM                | 14    | 60.17| 0.6664  | 0.6936(0.642, 0.74) |

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 | 0       | 10.59 (16.72) | 6.145 (3.76, 10.54) | < 0.0001 | - | 0.6371 (0.6043, 0.6456) |
| LNM   | 27  | 0       | 24.65 (23.68) | 15.51 (10.77, 32.66) | < 0.0001 | < 0.0001 | 0.8868 (0.8217, 0.9518) |
| DM    | 13  | 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, 61.25). 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).
| Count | Age | P value | ROC |
|-------|-----|---------|-----|
| | Female | Male | Female | Male | mean(SD) | median(25%,75%) | control vs | I vs | I vs | AUC(95% confidence interval) |
| Colorectal cancer | 2205 | 823 | 1382 | 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 | - | - | 0.6840(0.658,0.7099) |
| II | 795 | 280 | 515 | 61.44 | 62.10 | 11.82(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) | 8.825(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(7.74,61.25b) | < 0.0001 | < 0.0001 | - | 0.8612(0.8235,0.8999) |
| 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) | 4.883(6.11,16.67) | > 0.9999 | - | - | 0.60650(0.08769,1.125) |
| II | 13 | 3 | 10 | 47.67 | 53.90 | 11.15(8.7) | 7.895(5.74,16.02) | > 0.9999 | > 0.9999 | - | 0.60280(0.3338,0.8719) |
| III | 91 | 26 | 65 | 49.27 | 50.42 | 10.91(13.63) | 6.393(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) | 7.934(3.32,15.42) | < 0.0001 | > 0.9999 | - | 0.70980(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) | 6.1364(10.83) | < 0.0001 | - | - | 0.6301(0.6073,0.6528) |
| II | 28 | 4 | 24 | 63.25 | 60.75 | 15.46(33.41) | 4.673(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) | 5.53(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) | 9.444(4.92,22.84) | < 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) | 6.324(4.09,10.76) | < 0.0001 | - | - | 0.6520(0.6226,0.6813) |
| II | 434 | 434 | 0 | 52.58 | 0 | 11.37(15.01) | 7.44(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) | 5.883(9.3,10.86) | 0.0606 | > 0.9999 | - | 0.6215(0.5142,0.7289) |
| IV | 15 | 15 | 0 | 48.27 | 0 | 26.04(47.08) | 8.116(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) | 5.012(2.78,8.04) | 0.3158 | - | - | 0.5475(0.4938,0.6012) |
| II | 55 | 4 | 51 | 66.75 | 63.73 | 5.74(4.4) | 4.052(3.78,8.63) | > 0.9999 | > 0.9999 | - | 0.5038(0.4182,0.5894) |
| III | 44 | 1 | 43 | 40.00 | 64.84 | 6.12(4.23) | 5.062(2.99,15.15) | > 0.9999 | > 0.9999 | - | 0.5468(0.4536,0.64) |
| IV | 38 | 1 | 37 | 74.00 | 63.76 | 10.41(12.5) | 5.894(4.14,10.19) | 0.0168 | 0.6204 | - | 0.6380(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               |
|---------------------|-------|------|---------|-------------------|
| **Bladder cancer**  |       |      |         |                   |
| I                   | 20    | 18   | > 0.999 | - 0.5020         |
| II                  | 14    | 0    | 0.1614  | 0.7376           |
| III                 | 11    | 2    | 0.3551  | 0.6199           |
| IV                  | 21    | 6    | 0.006   | 0.0955           |
| **Renal carcinoma** |       |      |         |                   |
| I                   | 46    | 13   | 0.269   | - 0.5624         |
| II                  | 10    | 5    | > 0.999 | > 0.999          |
| III                 | 17    | 5    | 0.3551  | > 0.999          |
| IV                  | 22    | 8    | 0.014   | 0.8486           |
| **Esophagus cancer**|       |      |         |                   |
| I                   | 99    | 26   | 0.1949  | 0.5624(0.5103, 0.6144) |
| II                  | 241   | 42   | 0.0094  | 0.5643(0.5249, 0.6037) |
| III                 | 187   | 21   | < 0.001 | > 0.999          |
| IV                  | 20    | 3    | 0.6519  | > 0.999          |
| **Gastric cancer**  |       |      |         |                   |
| I                   | 1031  | 316  | 0.0008  | 0.6295(0.5901, 0.669) |
| II                  | 191   | 67   | < 0.001 | < 0.4399         |
| III                 | 496   | 139  | < 0.001 | < 0.0001         |
| IV                  | 102   | 45   | < 0.001 | < 0.0001         |
| **Endometrial cancer** |      |      |         |                   |
| I                   | 104   | 104  | 9.3 (6.2725, 14.5) | - 0.8508(0.8073, 0.8942) |
| II                  | 85    | 85   | 0.0008  | 0.6228(0.5594, 0.6863) |
| III                 | 4     | 4    | 0.0402  | 0.3852           |

**SD standard deviation**

The ROC were constructed for stage I, stage II, stage III or stage IV vs healthy control
Table 4

| Count | Age | P value | ROC |
|-------|-----|---------|-----|
| 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 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

| Count | Age | P value | ROC |
|-------|-----|---------|-----|
| 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 small 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 Huaqian 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, lung cancer, cervical cancer, stomach cancer, endometrial cancer, prostate cancer, and pancreatic cancer patients were significantly higher than those in healthy controls (Table 1), indicating that CA242 has potential clinical value in these diseases. Although mediasinal cancer, testicular cancer, ureteral cancer, and neuroendocrine cancer patients had higher mean and median values than healthy 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, perianal 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, 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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36. Recurrence after Resection for Ductal Adenocarcinoma of the Pancreas.
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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- SupplementalTable3.docx
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