Introduction
Colorectal cancer (CRC) ranked third in incidence and second in mortality according to the global cancer statistics in 2020 [1]. Environmental and genetic factors (gene mutations, chromosomal abnormalities, and epigenetic changes) are involved in CRC development [2]. Microsatellite instability (MSI) is caused by the impaired DNA mismatch repair system, including high MSI (MSI-H) and low MSI (MSI-L). MSI CRC is characterized by a high density of tumor-infiltrating lymphocytes located in the proximal colon, and a better prognosis than microsatellite stabilization (MSS) tumors, accounting for 15% in CRC without a family history [3, 4]. Tumors can induce platelet activation, and activated platelets could promote tumor progression and metastasis [5]. Mean platelet volume (MPV) is considered an indicator of platelet activation and decreased MPV is a poor prognostic marker for many cancers [6–8]. MPV is significantly reduced in the MSI-H subtype of CRC [9, 10].

C-type lectin-like receptor 2 (CLEC-2) is a type II transmembrane protein. It is mainly expressed on activated platelets and megakaryocytes and released into plasma after platelet activation [11]. Podoplanin, the only established endogenous ligand for CLEC-2, is described on the surface of tumors or lymphatic endothelial cells and stimulates platelet activation through CLEC-2.
binding to promote blood-borne tumor metastasis or the separation of blood/lymphatic vessels at the developmental stage [12]. However, few studies evaluated CLEC-2 levels in patients with CRC. This study aimed to determine the plasma levels of CLEC-2 in CRC patients and investigate the associations between CLEC-2 levels and MSI status.

Methods
Study population
CRC patients aged 18 years and over were invited to participate in this cross-sectional study in Harbin Medical University Cancer Hospital from January 2018 to December 2018. CRC was identified by histology. Patients were excluded with the following condition: (1) any history of radiotherapy, chemotherapy, or other anti-cancer therapy; (2) infection, hematological disorders, hypertension, and diabetes mellitus; (3) medical treatment with statins and acetylsalicylic acid; (4) insufficient clinical data. The trained research assistant collected data about age, gender, body mass index (BMI), smoking status, and drinking status of all eligible participants with a well-designed questionnaire.

The clinical data were collected and recorded based on the medical system records, including albumin, creatinine, white blood cells (WBC), hemoglobin, platelet count, tumor location, tumor size, histological type, histological grade, venous invasion, perineural invasion, T classification, lymph node metastasis, and distant metastasis. The TNM stage was classified according to the 8th edition of the American Joint Committee on Cancer staging system.

CLEC-2 measurements
A venous blood sample was drawn from each participant under fasting conditions at primary diagnosis before any treatment. The blood samples were collected by tubes containing sodium citrate and separated by centrifugation at 2500 rpm for 10 minutes, and the plasma was stored at −80°C until enzymatic analysis. CLEC-2 levels were measured in the hospital clinical laboratory, using commercially available sandwich ELISA kits (Xinle, Shanghai, China, respectively). Samples were measured as duplicates. The intra- and inter-assay variations were below 8 and 10%, respectively.

MSI analysis
The MSI was evaluated with DNA obtained from fresh frozen tumor tissue samples, using polymerase chain reaction with primers amplifying the microsatellite markers (BAT25, BAT26, NR-21, NR-24, and NR-27). MSI was defined as ≥3 unstable markers, while MSS was <3 unstable markers. No sample has only two unstable markers.

Statistical analysis
The numbers and percentages were reported for presenting categorical variables. The mean ± standard deviation (SD) was used for reporting normal distribution continuous data, and the median (interquartile range) for non-normally distributed data. The Student’s t test was used when comparing variables with normal distribution in two groups, and the Mann-Whitney U test for skewed-distributed data. The χ² test was used to evaluate the differences of categorical variables between groups. Binary logistic regression was used to assess the association between clinicopathological factors with MSI-H status. A receiver operating characteristic (ROC) curve was drawn to determine a threshold value of CLEC-2 for differentiating MSS from MSI-H using MedCalc version 15.0. SPSS Statistics version 25.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, and p < 0.05 represents statistical significance.

Results
A total of 430 eligible CRC patients were included in the final analysis, of which 14.88% were MSI-H patients. Baseline characteristics were compared between patients with MSI-H and MSS. CRC patients with MSI-H had higher BMI, WBC, CLEC-2 levels, younger age and lower hemoglobin levels than patients with MSS (Table 1). MSI-H status was significantly associated with tumor staging system.

| Variables | MSI-H | MSS | p value |
|-----------|-------|-----|---------|
| Number    | 64    | 366 |         |
| Age (years) | 56.4 ± 11.8 | 59.9 ± 9.6 | 0.029* |
| Female (n, %) | 33 (51.6) | 148 (40.4) | 0.096 |
| BMI (kg/m²) | 24.5 ± 3.3 | 23.2 ± 3.2 | 0.004** |
| Current smoker (%) | 25 (39.1) | 158 (43.2) | 0.540 |
| Drinker (n, %) | 17 (26.6) | 159 (33.3) | 0.285 |
| Creatinine (umol/L) | 80.9 ± 19.7 | 81.1 ± 18.4 | 0.829 |
| WBC (× 10³/µL) | 8.07 ± 2.98 | 6.92 ± 2.30 | 0.004** |
| Hemoglobin (g/L) | 124.6 ± 27.3 | 134.3 ± 22.4 | 0.009** |
| Platelet count (× 10³/µL) | 286.2 ± 112.6 | 266.8 ± 82.6 | 0.191 |
| CLEC-2 (pg/mL) | 166.1 ± 41.3 | 133.5 ± 36.1 | < 0.001*** |

Values are means ± SD, median with interquartile range, or number with percentage

BMI body mass index, WBC white blood cells, CLEC-2 c-type lectin-like receptor 2, MSI-H high microsatellite instability, MSS microsatellite stable

*p < 0.05; **p < 0.01; ***p < 0.001 vs. the values of MSS group
location, tumor size, lymphatic invasion, lymph node metastasis, clinical stage, and histological type (Table 2).

The median value of CLEC-2 was 138.3 (range, 62.0–272.6). The optimal cutoff value determined by ROC analysis for the CLEC-2 was 166.3 for the MSI-H (Fig. 1). The specificity and sensitivity were 51.6 and 86.9%, respectively (AUC = 0.734, 95% CI: 0.663–0.805, \( p < 0.001 \)). CRC patients were divided into two groups according to the cutoff value. Of the 430 patients, 81 patients (18.8%) were detected with CLEC-2 of greater than 166.3 pg/mL, while there were 349 patients (81.2%) whose CLEC-2 levels were less than or equal to 166.3 pg/mL. Association between CLEC-2 and clinicopathologic variables was presented in Table 3. There were significant differences between CLEC-2 levels and MSI status.

All CRC patients were classified into quartiles according to their CLEC-2 levels, including quartile 1 (Q1) \( \leq 104.7 \) pg/mL, 104.7 pg/mL < quartile 2 (Q2) \( \leq 142.7 \) pg/mL, 142.7 pg/mL < quartile 3 (Q3) \( \leq 157.6 \) pg/mL, and quartile 4 (Q4) > 157.6 pg/mL (Fig. 2). The percentages of CRC patients with MSI-H in each group were 5.6, 8.2, 13.1 and 33.0%, respectively. The results showed that the percentage of patients with MSI-H increased according to CLEC-2 levels.

Logistic regression analysis was performed to evaluate the clinicopathological factors associated with MSI-H status. Eleven variables, including age, BMI, WBC, hemoglobin, CLEC-2, tumor size, tumor location, lymphatic invasion, histological type, lymph node metastasis, and clinical stage, were entered into the original equation. The factors significantly associated with MSI-H in the regression analysis included age, BMI, WBC, CLEC-2, tumor size, tumor location, lymphatic invasion, histological type, and clinical stage, were entered into the original equation. The factors significantly associated with MSI-H in the regression analysis included age, BMI, WBC, CLEC-2, tumor size, tumor location, lymphatic invasion, histological type, and clinical stage, were entered into the original equation. The factors significantly associated with MSI-H in the regression analysis included age, BMI, WBC, CLEC-2, tumor size, tumor location, and histological type (Table 4). Notably, higher CLEC-2 levels were associated with MSI-H after adjusting for other confounding variables.

**Table 2** Clinicopathological features of colorectal cancer patients according to microsatellite instability status

| Variables                  | Total | MSI-H | MSS | \( p \) value |
|----------------------------|-------|-------|-----|--------------|
| Tumor location             |       |       |     | < 0.001***   |
| Proximal                   | 150 (34.9) | 38 (59.4) | 112 (30.6) | |
| Distal                     | 280 (65.1) | 26 (40.6) | 254 (69.4) | |
| Tumor size (cm)            |       |       |     | 0.011*       |
| < 5.0                      | 282 (65.6) | 33 (51.6) | 249 (68.0) | |
| ≥ 5.0                      | 148 (34.4) | 31 (48.4) | 117 (32.0) | |
| Histological grade         |       |       |     | 0.254        |
| Well/Moderately differentiated | 314 (73.0) | 43 (67.2) | 271 (74.0) | |
| Poorly differentiated       | 116 (27.0) | 21 (32.8) | 95 (26.0)  | |
| Histological type          |       |       |     | 0.001**      |
| Non‑mucinous               | 368 (85.6) | 46 (71.9) | 322 (88.0) | |
| Mucinous                   | 62 (14.4)  | 18 (28.1) | 44 (12.0)  | |
| Lymphatic invasion         |       |       |     | 0.030*       |
| Absent                     | 331 (77.0) | 56 (87.5) | 275 (75.1) | |
| Present                    | 99 (23.0)  | 8 (12.5)  | 91 (24.9)  | |
| Perineural invasion        |       |       |     | 0.527        |
| Absent                     | 365 (84.9) | 56 (87.5) | 309 (84.4) | |
| Present                    | 65 (15.1)  | 8 (12.5)  | 57 (15.6)  | |
| T classification           |       |       |     | 0.811        |
| T1 + T2                    | 63 (14.7)  | 10 (15.6) | 53 (14.5)  | |
| T3 + T4                    | 367 (85.3) | 54 (84.4) | 313 (85.5) | |
| Lymph node metastasis      |       |       |     | 0.010**      |
| Absence                    | 267 (62.1) | 49 (76.6) | 218 (59.6) | |
| Presence                   | 163 (37.9) | 15 (23.4) | 148 (40.4) | |
| Distant metastasis         |       |       |     | 0.713        |
| Absence                    | 382 (88.8) | 56 (87.5) | 326 (89.1) | |
| Presence                   | 48 (11.2)  | 8 (12.5)  | 40 (10.9)  | |
| Stage                      |       |       |     | 0.003**      |
| I–II                       | 258 (60.0) | 49 (76.6) | 209 (57.1) | |
| III–IV                     | 172 (40.0) | 15 (23.4) | 157 (42.9) | |

Values are number with percentage. Abbreviation as in Table 1. *p < 0.05; **p < 0.01; ***p < 0.001 vs. the values of MSS group.

**Discussion**

The current finding showed that CLEC-2 levels were strongly associated with MSI-H CRC after adjusting the confounding confounders.
Table 3  Baseline characteristics of colorectal cancer patients according to c-type lectin-like receptor 2 levels

| Variables                      | Total     | CLEC-2 ≤ 166.3 | CLEC-2 > 166.3 | p value  |
|--------------------------------|-----------|----------------|----------------|----------|
| Age (years)                    | 0.298     |                |                |          |
| ≤ 65                           | 309 (71.9)| 247 (70.8)     | 62 (76.5)      |          |
| > 65                           | 121 (28.1)| 102 (29.2)     | 19 (23.5)      |          |
| Gender                         | 0.432     |                |                |          |
| Male                           | 245 (57.0)| 202 (57.9)     | 43 (53.1)      |          |
| Female                         | 185 (43.0)| 147 (42.1)     | 38 (46.9)      |          |
| BMI (kg/m²)                    | 0.166     |                |                |          |
| 23.4 ± 3.2                    | 23.9 ± 3.2| 23.3 ± 3.2     |                |          |
| Current smoker                 | 0.906     |                |                |          |
| Yes                            | 183 (42.6)| 149 (42.0)     | 34 (42.0)      |          |
| No                             | 247 (57.4)| 200 (58.0)     | 47 (58.0)      |          |
| Drinker                        | 0.401     |                |                |          |
| Yes                            | 139 (32.3)| 116 (33.2)     | 23 (28.4)      |          |
| No                             | 291 (67.7)| 233 (66.8)     | 58 (71.6)      |          |
| WBC (x 10^9/L)                 | 0.393     |                |                |          |
| 7.09 ± 2.44                   | 7.35 ± 3.16| 7.03 ± 2.25    |                |          |
| Hemoglobin (g/L)               | 0.141     |                |                |          |
| 132.9 ± 23.4                  | 129.4 ± 25.2| 133.7 ± 23.0  |                |          |
| Platelet count (x 10^11/L)     | 0.093     |                |                |          |
| 270.0 ± 87.8                  | 265.6 ± 82.8| 286.9 ± 105.7 |                |          |
| Creatinine (umol/L)            | 0.467     |                |                |          |
| 81.1 ± 18.6                   | 83.0 ± 28.4| 80.6 ± 15.4    |                |          |
| CEA (ng/ml)                    | 0.788     |                |                |          |
| 4.37 (2.03–11.31)             | 3.82 (1.94–13.70)| 4.67 (2.12–106.7)|          |
| Tumor size (cm)                | 0.260     |                |                |          |
| < 5.0                          | 278 (64.7)| 230 (65.9)     | 48 (59.3)      |          |
| ≥ 5.0                          | 152 (35.3)| 119 (34.1)     | 33 (40.7)      |          |
| Tumor location                 | 0.687     |                |                |          |
| Proximal                       | 157 (36.5)| 129 (37.0)     | 28 (34.6)      |          |
| Distal                         | 273 (63.5)| 220 (63.0)     | 53 (65.4)      |          |
| Histological type              | 0.835     |                |                |          |
| Non-mucinous                   | 359 (83.5)| 294 (84.2)     | 65 (80.2)      |          |
| Mucinous                       | 71 (28.6)| 55 (15.8)      | 16 (19.8)      |          |
| Histological grade             | 0.835     |                |                |          |
| Well/Moderately differentiated  | 359 (83.5)| 292 (83.7)     | 67 (82.7)      |          |
| Poorly differentiated           | 71 (28.6)| 57 (16.3)      | 14 (17.3)      |          |
| Lymphatic invasion             | 0.285     |                |                |          |
| Absent                         | 331 (77.0)| 265 (75.9)     | 66 (81.5)      |          |
| Present                        | 99 (23.0)| 84 (24.1)      | 15 (18.5)      |          |
| Perineural invasion            | 0.545     |                |                |          |
| Absent                         | 365 (84.9)| 298 (85.4)     | 67 (82.7)      |          |
| Present                        | 65 (15.1)| 51 (14.6)      | 14 (17.3)      |          |
| T classification               | 0.693     |                |                |          |
| T1 + T2                        | 63 (14.7)| 50 (14.3)      | 13 (16.0)      |          |
| T3 + T4                        | 367 (85.3)| 299 (85.7)     | 68 (84.0)      |          |
| Lymph node metastasis          | 0.665     |                |                |          |
| Absence                        | 267 (62.1)| 215 (61.6)     | 52 (64.2)      |          |
| Presence                       | 163 (37.9)| 143 (38.4)     | 29 (35.8)      |          |
| Distant metastasis             | 0.707     |                |                |          |
| Absence                        | 382 (88.8)| 311 (89.1)     | 71 (87.7)      |          |
| Presence                       | 48 (11.2)| 38 (10.9)      | 10 (12.3)      |          |
| Stage                          | 0.392     |                |                |          |
| II                             | 258 (60.0)| 206 (59.0)     | 52 (64.2)      |          |
| III                            | 172 (40.0)| 143 (41.0)     | 29 (35.8)      |          |
| MSI status                     | <0.001*** |                |                |          |
| MSS                            | 366 (85.1)| 318 (91.1)     | 48 (59.3)      |          |
| MSI-H                          | 64 (14.9)| 31 (8.9)       | 33 (40.7)      |          |

Values are means ± SD, median with interquartile range, or number with percentage. MSI, microsatellite instability; Other abbreviation as in Table 1. ***p < 0.001 vs. the values of CLEC-2 > 166.3 group
As one of the most common cancer, the global burden of CRC is expected to increase by 60% in 2030 [13]. CRC is characterized by the gradual accumulation of malignant transformation involving multiple genetic changes, which is conducive to the proliferation and growth of tumor cells [14]. MMR is an important mechanism used by cells to repair damaged DNA. MMR recognizes and repairs DNA base insertions, deletions, and mismatches, which are caused by DNA polymerase slippage during replication [15]. Compared with normal cells, the mutation rate of cancer cells with MMR is 100 to 1000 times that of normal cells. MSI-H tumors tend to be mucinous and poorly differentiated, with an expansive growth pattern, histological heterogeneity, and tumor-infiltrating lymphocytes [15].

The exact mechanisms of CLEC-2 in MSI-H CRCs are currently unclear. Both CLEC-2 and microsatellite status have been confirmed to be related to platelet activation status, which may be their underlying mechanism [10, 11]. CLEC-2 plays an important role in body development, tumor progression and immune response [16]. In malignant tumors, CLEC-2 and podoplanin work together to activate platelets to promote tumor metastasis and promote tumor-related thrombosis [12]. The difference of CLEC-2 in different CRC subtypes supports the crucial roles that platelets play in immune cells. Previous studies showed that the CD8 T effector gene signature was significantly upregulated in MSI-H tumors compared with MSI-L/MSS tumors [17]. The abundance of podoplanin is related to the immune evasion environment characterized by the infiltration of tumor macrophages and dysfunctional CD8+ T cells [18]. The growth and progression of tumors are also affected by the abundant tumor-associated macrophages in the tumor microenvironment [19]. MSI-H and MSI-L CRC have different tumor microenvironments. MSI-H tumor cells are characterized by their high mutation rate leading to the presentation of mutant peptides on their major histocompatibility complex class I molecules. These processes, in turn, are recognized by immune cells as foreign neoantigens, leading to a high density of cytotoxic CD8+ T cells infiltration and increased levels of IFN-γ secretion. Moreover, CD8 (+) cytotoxic T lymphocytes may increase platelet destruction in immune thrombocytopenia [20].

The tumor cells coated by aggregates of platelets are easy to evade the immune system and adhere to the vessel wall [5]. The activated platelets also secrete various bioactive factors that assist in extravasation to new metastatic sites [21]. Podoplanin has been reported to contribute to cancer pathogenesis by promoting tumor cell invasion and spreading [22]. The increased podoplanin expression was observed in patients with colorectal adenocarcinoma [23]. Clustering of podoplanin by platelet CLEC-2 regulates several molecular pathways involved in tumor cell migration and invasion [24]. Increased plasma CLEC-2 levels were observed in acute coronary syndrome, thrombotic microangiopathy, and acute ischemic stroke, indicating the critical role of CLEC-2 in thrombo-inflammation [25–27].

Table 4 Associations between clinical factors and microsatellite instability status

| Variables                      | β     | OR (95% CI)       | p value |
|--------------------------------|-------|-------------------|---------|
| Age (years)                    | −0.040| 0.961 (0.930–0.993)| 0.019*  |
| BMI (kg/m²)                    | 0.147 | 1.159 (1.049–1.280)| 0.004** |
| WBC (×10³/L)                   | 0.141 | 1.151 (1.022–1.296)| 0.020*  |
| Hemoglobin (g/L)               | −0.006| 0.994 (0.981–1.007)| 0.358   |
| CLEC-2 (pg/mL) (< 166.3 vs > 166.3) | 2.096 | 8.132 (4.047–16.341)| < 0.001*** |
| Tumor size (cm)                | 0.949 | 2.582 (1.332–5.006)| 0.005** |
| (> 5.0 cm vs ≤ 5.0 cm)         |      |                   |         |
| Tumor location (Proximal vs Distal) | 1.373 | 3.948 (1.968–7.920)| < 0.001*** |
| Histological type (Mucinous vs Non-mucinous) | 1.037 | 2.820 (1.286–6.187)| 0.010*   |
| Lymphatic invasion (Presence vs Absence) | −0.365 | 0.694 (0.267–1.806)| 0.455   |
| Lymph node metastasis (Presence vs Absence) | 0.219 | 1.245 (0.133–11.663)| 0.848   |
| Stage (III+IV vs I+II)         | −1.031| 0.357 (0.039–6.228)| 0.359   |

Values are logistic regression coefficient and odds ratio with 95% confidence interval. β, logistic regression coefficient; OR odds ratio, CI confidence interval; other abbreviation as in Table 1. *p < 0.05; **p < 0.01; ***p < 0.001 vs. the values of MSS group.
This study has some potential limitations: Firstly, our results were sourced from a single hospital. Secondly, further study is needed to explain our results mechanistically. Finally, this study only included Chinese participants, and the current finding should be validated in other populations.

Conclusions
Increased CLEC-2 is associated with the MSI-H subtype of CRC. Further mechanistic research was needed.

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Not applicable.

Authors' contributions
Xin Zhang and Jiayu Yuan proposed and designed the study; Xin Wang and Shuang Fu collected data, Rui-tao Wang and Guang-yu Wang analyzed the data, interpreted the results, and drafted the article. Every author approved the final version of the manuscript for publishing.

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Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due to privacy or ethical restrictions in our institute but are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Harbin Medical University Cancer Hospital (2019‑06). Consent for publication
Written informed consent.

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

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References
1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998;58(22):5248–57.
4. Motta R, Cabezas-Camarero S, Torres-Mattos C, Riquelme A, Calle A, Figueroa A, et al. Immunotherapy in microsatellite instability metastatic colorectal cancer: Current status and future perspectives. J Clin Transl Res. 2021;7(4):511–22.
5. Gaertner F, Massberg S. Patrolling the vascular borders: platelets in immunity to infection and cancer. Nat Rev Immunol. 2019;19(12):747–60.
6. Wu YY, Zhang X, Qin YY, Qin JQ, Lin FQ. Mean platelet volume/platelet count ratio in colorectal cancer: a retrospective clinical study. BMC Cancer. 2019;19(1):314.
7. Yin JB, Niu Y, Qian LY, Zhang X, Liu ZP, Wang RT. Mean platelet volume predicts survival in patients with hepatocellular carcinoma and type 2 diabetes. Diabetes Res Clin Pract. 2019;151:120–7.
8. Bv P, Anwar AZ, Harsha R, Arakani PR, Jonnada P. Role of Mean Platelet Volume in the Prognosis of Gallbladder Carcinoma: A Tertiary Centre Experience. Cureus. 2021;13(7):e16389.
9. Wang W, Wang G, Fu S, Zhang B, Liu Z, Wang R. Decreased mean platelet volume is associated with microsatellite instability in colorectal cancer: A propensity score-matched analysis. Cancer Biomark. 2021;31(4):351–9.
10. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: methodological issues. Platelets. 2002;13(5–6):301–6.
11. Kazama F, Nakamura J, Osada M, Inoue O, Oosawa M, Tamura S, et al. Measurement of soluble C-type lectin-like receptor 2 in human plasma. Platelets. 2015;26(9):711–9.
12. Suzuki-Inoue K. Platelets and cancer-associated thrombosis: focusing on the platelet activation receptor CLEC-2 and podoplanin. Blood. 2019;134(22):1912–8.
13. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683–91.
14. Fearon ER. Molecular genetics of colorectal cancer. Annu Rev Pathol. 2011;6:479–507.
15. Kreidieh M, Muhkerji D, Temraz S, Shamseddine A. Expanding the Scope of Immunotherapy in Colorectal Cancer: Current Clinical Approaches and Future Directions. Biomed Res Int. 2020;2020:9037217.
16. Brown GD, Willment JA, Whitehead L. C-type lectins in immunity and homeostasis. Nat Rev Immunol. 2018;18(6):374–89.
17. Kikuchi T, Mimura K, Okayama H, Nakayama Y, Saito K, Yamada L, et al. A subset of patients with MSS/MSI-low colorectal cancer showed increased CD8(+)-TILs together with up-regulated IFN-gamma. Oncol Lett. 2019;18(6):5977–85.
18. Liu X, Cao Y, Lv K, Gu Y, Jin K, He X, et al. Tumor-infiltrating podoplanin(+) cells in gastric cancer: clinical outcomes and association with immune contexture. Oncoimmunology. 2020;9(1):184038.
19. Zhou Q, Wang Z, Zeng H, Zhang H, Liu Z, Huang Q, et al. Identification and validation of poor prognosis immunoevasive subtype of muscle-invasive bladder cancer with tumor-infiltrating podoplanin(+) cell abundance. Oncoimmunology. 2020;9(1):1747333.
20. Qiu J, Liu X, Li X, Wang Z, Han P, Zhou H, et al. CD8(+)-T cells induce platelet clearance in the liver via platelet desialylation in immune thrombocytopenia. Sci Rep. 2016;6:27445.
21. Catani MV, Savini I, Tullio V, Gasperi V. The “Janus Face” of Platelets in Acute Ischemic Stroke. Stroke. 2018;50:STROKEAHA11802563.
22. Suzuki-Inoue K. Roles of the CLEC-2-podoplanin interaction in tumor progression. Platelets. 2018;129:411–7.
23. Kato Y, Fujita N, Kunita A, Sato S, Kaneko M, Osawa M, et al. Molecular identification of Aggsrus/T1 alpha as a platelet aggregation-inducing factor expressed in colorectal tumors. J Biol Chem. 2003;278(15):15999–6005.
24. Lowe KL, Navarro-Nunez L, Watson SP. Platelet CLEC-2 and podoplanin in cancer metastasis. Thromb Res. 2012;129(Suppl 1):S30–7.
25. Inoue O, Osada M, Nakamura J, Kazama F, Shirai T, Tsukui J, et al. Soluble CLEC2 (C-Type Lectin-Like Receptor 2) in Patients With Acute Ischemic Stroke. Stroke. 2018;50:STROKEAHA118022563.