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Research article

Clinical atlas of rectal cancer highlights the barriers and insufficient interventions underlying the unfavorable outcomes in older patients

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ABSTRACT

Background: Aging confers an increased risk of developing cancer, and the global burden of cancer is cumulating as human longevity increases. Providing adequate care for old patients with rectal cancer is challenging and complex.

Method: A total of 428 and 44,788 patients diagnosed with non-metastatic rectal cancer from a referral tertiary care center (SYSU cohort) and the Surveillance Epidemiology and End Results database (SEER cohort) were included. Patients were categorized into old (over 65 years) and young (aged 50–65 years) groups. An age-specific clinical atlas of rectal cancer was generated, including the demographic and clinicopathological features, molecular profiles, treatment strategies, and clinical outcomes.

Results: Old and young patients were similar in clinicopathological risk factors and molecular features, including TNM stage, tumor location, tumor differentiation, tumor morphology, lymphovascular invasion, and perineural invasion. However, old patients had significantly worse nutritional status and more comorbidities than young patients. In addition, old age was independently associated with less systemic cancer treatment (adjusted odds ratio 0.294 [95% CI 0.184–0.463, $P < 0.001$]). We found that old patients had significantly worse overall survival (OS) outcomes in both SYSU ($P < 0.001$) and SEER ($P < 0.001$) cohorts. Moreover, the death and recurrence risk of old patients in the subgroup not receiving chemo/radiotherapy ($P < 0.001$ for OS, and $P = 0.046$ for time to recurrence [TTR]) reverted into no significant risk in the subgroup receiving chemo/radiotherapy.

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Conclusions: Although old patients had similar tumor features to young patients, they had unfavorable survival outcomes associated with insufficient cancer care from old age. Specific trials with comprehensive geriatric assessment for old patients are needed to identify the optimal treatment regimens and improve unmet cancer care.
Study registration: The study was registered on the research registry with the identifier of researchregistry 7635.

1. Introduction

The global population has aged quickly in recent decades, imposing a booming burden of diseases, including heart disease, severe COVID-19, diabetes, and cancer [1–3]. Cancer is expected to become more prevalent among them and reach 34 million new cases in 2070, particularly in old patients [4]. Cancer is a disease of aging and a leading cause of death in the population older than 65 [5]. It has been estimated that more than half of all cancers and over 70% of deaths associated with cancer occur in old patients [6]. About 6.7 million new cancer cases were diagnosed in 2012, which was projected to double by 2035 (14.0 million) among old adults [7]. Colorectal cancer is a leading tumor, with nearly 1.2 million newly diagnosed cases and 660,000 deaths worldwide in 2020 [8]. Approximately 68.1% of colorectal cancer deaths occur in old patients over 65 [9]. Importantly, the proportion of rectal cancer has increased among colorectal cancer patients in past decades [10].

Providing adequate and appropriate care for old cancer patients is under urgent need. However, old patients with rectal cancer receive less cancer treatment [11,12]. The systemic treatment recommended by current guidelines for rectal cancer includes chemotherapy, radiotherapy, targeted therapy and immunotherapy. However, the lack of recruitment of old patients in previous clinical trials leads to the dilemma that there is no sufficient evidence to guide clinical treatment decisions in geriatric rectal cancer patients [13–18]. Thus, it has been advocated that specific strategies be developed to include geriatric patients in observative studies and intervention trials and bridge the data-free zone in this unique population to generate specific evidence for treatment [19].

Therefore, a comprehensive characterization of old patients with rectal cancer may help clinicians design future trials on the decision-making process. In this study, we generated a clinical atlas of old patients with rectal cancer and identified the specific clinicopathological features, treatment strategies and outcomes in cancer care for old patients to provide insights into geriatric management.

2. Methods

2.1. Study population

A total of 18,013 patients who were pathologically diagnosed with colorectal cancer at the Sixth Affiliated Hospital of Sun Yat-sen University (SYSU) between June 2007 and June 2012 were identified for patient inclusion in the SYSU cohort. We prospectively collected demographic and baseline clinicopathological features, treatment strategies, and short- and long-term treatment outcomes, including commonly occurring postoperative complications such as anastomotic leakage, anastomotic bleeding, anastomotic stenosis, abscesses, fistulas, and fever, as well as long-term recurrence. These data were collected in accordance with the guidelines from the Institutional Database Program of Colorectal Disease (IDPCD), as previously described [20–22]. The SYSU cohort originates from the southern China population, and the patients were treated and followed up according to the National Comprehensive Cancer Network guideline-based protocol as previously described [22–26]. Moreover, we analyzed the colorectal cancer patients aged over 50 years diagnosed between 1992 and 2015 from the SEER database (Incidence-SEER Research Date, 9 Registries, Nov 2020 Sub (1975–2018)) [27] to validate the findings in the SYSU cohort. The dataset obtained from the SEER database was identified as "Site Recode ICD-*O*-3/WHO 2008″ with a focus on the site group "Rectum" and ICD-*O*-3 site C209. We included the stage I to III rectal cancer patients aged over 50 years in both SYSU and SEER cohorts. Patients were divided into young and old groups according to the cut-off of 65 years. To avoid the impact of young-onset rectal cancer with well-documented distinct clinical features on the analysis [28], we excluded patients aged less than 50 years. In addition, patients with documented adenomatous polyposis (FAP) or other hereditary colorectal cancers were excluded. The patient disposition flow in each cohort was summarized in Figure S1.

2.2. Molecular phenotyping

The paraffin-embedded formalin-fixed (FFPE) tumor tissue specimens were used to extract DNA for molecular phenotyping in the SYSU cohort. The status of mismatch repair (proficient-MMR, pMMR/deficient-MMR, dMMR) was assessed based on immunohistochemistry testing of MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MutS homolog 6 (MSH6), and Postmeiotic segregation increased 2 (PMS2) [29,30]. The hotspot mutations in *B-Raf proto-oncogene serine/threonine kinase (BRAF)* p.V600E and *Kirsten rat sarcoma viral oncogene homolog (KRAS)* codons 12 and 13 were identified through Sanger sequencing [31,32]. CpG island methylator phenotype (CIMP) was determined by the quantitative methylation-specific PCR assay using the Weisenberger's panel including calcium voltage-gated channel subunit alpha1 G (CACNA1G), insulin-like growth factor 2 (IGF2), neurogenin 1 (NEUROG1), runt-related transcription factor 3 (RUNX3) and suppressor of cytokine signaling 1 (SOCS1) as previously described [33,34].

2.3. Evaluation of tumor-infiltrating lymphocytes

The slides cut from the FFPE tumor tissue block were used to evaluate the tumor-infiltrating lymphocytes (TILs). We first evaluated the overall TILs using the hematoxylin-eosin (HE)-stained slides according to the morphology-based method recommended by the International TILs Working Group [35]. To evaluate $CD8^+$ TILs, we used the monoclonal anti-CD8 antibody and the secondary antibody conjugated with horseradish peroxidase to perform an immunohistochemical assay following the methods described in the previous study [20]. The average cell count in the assessed view fields was compared between the two age groups.

2.4. Statistical analysis

The analysis with variance or Wilcoxon test for numerical variables was performed for group comparison, and the chi-square or two-tailed Fisher's exact test was used for categorical variables. We used the Logistic regression model to analyze the association of old age with absent chemo/radiotherapy in the SYSU cohort, age, sex, tumor stage, node stage, tumor differentiation, tumor morphology, lymphovascular invasion, and perineural invasion were included in the model. Associations of age groups were also assessed with respect to overall survival (OS) and time to recurrence (TTR), in which OS was defined as the time to death from any cause, and TTR was defined as the time to first documented disease recurrence. The inverse probability weighting (IPW) method [36,37] was used to calculate adjusted survival probability and generate each survival plot. In the SYSU cohort, age, sex, TNM stage, tumor location, tumor differentiation, tumor morphology, lymphovascular invasion, perineural invasion, baseline carcinoembryonic antigen (CEA), and

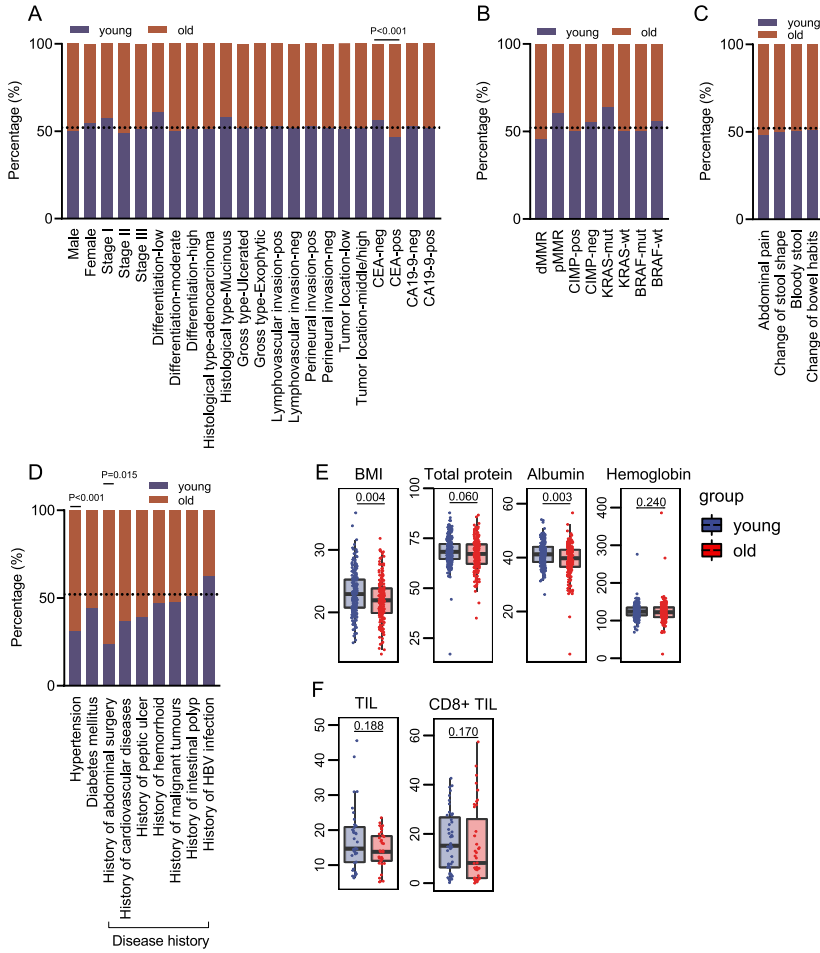

Fig. 1. Comprehensive characterization of young and old age rectal cancer patients. (A) Baseline characteristics of rectal cancer patients according to age (Supplementary Tab. 1); (B) Molecular subtypes distribution between two age groups (Supplementary Tab. 2); (C) Symptoms before diagnosis in the young and old age patients (Supplementary Tab. 3); (D) Distribution of comorbidities and disease history between young and old age patients (Supplementary Tab. 4); (E) Nutritional status of young and old age patients (Supplementary Tab. 5); (F)TIL and $CD8^+$ TIL counts of young and old age patients (Supplementary Tab. 5). CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; MSI, microsatellite instability; MSS, microsatellite stability; CIMP, CpG island methylator phenotype; BMI, body mass index (kg/m^2); Total protein (g/L); Albumin (g/L); Hemoglobin (g/L); TIL, tumor-Infiltrating lymphocyte (count).

treatment strategies were weighted by IPW method, while age, sex, tumor morphology, grade, stage, year of diagnosis, race and ethnicity and household income were weighted in SEER cohort. We also used Cox proportional hazards regression to evaluate the association of old age with survival outcomes, and the regression models included the same variables weighted in the IPW analyses. Data analyses were performed using the R software 4.1.2. P values < 0.05 were considered statistically significant with two-tailed tests.

3. Results

3.1. Overview of patient cohorts

A total of 428 and 44,788 patients were included in the SYSU and SEER cohorts, respectively. There were 223 young and 205 old patients in the SYSU cohort, and the two age groups in the SEER cohort had 17,088 and 27,700 patients, respectively. In the SYSU cohort, there were 255 male (59.6%) and 173 female (40.4%) patients, with a median age of 64 years (IQR: 57–71 years). In the SEER cohort, there were 25,994 male (58.0%) and 18,794 female (42.0%) patients, with a median age of 69 years (IQR: 60–77 years).

3.2. Old patients had more comorbidities with worse physical conditions

In the SYSU cohort, the incidence of hypertension (29.3% vs. 12.1%, $P < 0.001$) and frequency of the history of abdominal surgery (7.8% vs. 2.2%, $P = 0.015$) were significantly higher in old patients. In addition, the incidence of diabetes mellitus (14.1% vs. 10.3%, $P = 0.287$) and cardiocerebrovascular diseases (9.3% vs. 4.9%, $P = 0.117$) and frequency of the history of peptic ulcer (5.4% vs. 3.1%, $P = 0.365$), intestinal polyp (14.6% vs. 13.9%, $P = 0.938$) and malignant tumors (11.2% vs. 9.4%, $P = 0.650$) were higher in old patients. However, the difference was not significant (Fig. 1D). Taken together, we found that old patients had more comorbidities and a history of diseases.

Next, we investigated the nutritional status between the two age groups. Significantly lower baseline BMI (median: 21.92 vs. 22.92 kg/m^2, $P = 0.004$) and albumin (median: 39.75 g/L vs. 41.20, $P = 0.003$) were found before surgical treatment in old patients (Fig. 1E).

Old patients are similar to young patients in clinicopathological features and tumor biology.

We first analyzed the clinical features before diagnosis in old patients with rectal cancer. The old patients were similar to young patients in the incidence of symptoms before diagnosis, including abdominal pain, weight loss, change of bowel habits, change of stool shape and bloody stool (Fig. 1C).

Next, we analyzed the clinicopathological features between the two age groups. No significant differences were found between old and young patients regarding TNM stage, tumor location, tumor differentiation, tumor morphology, lymphovascular invasion and perineural invasion, that are well-documented risk factors associated with survival outcomes. However, the elevated baseline CEA was significantly more prevalent in old patients (36.8% vs. 28.2%, $P < 0.001$) (Fig. 1A).

Finally, we compared the molecular subtypes and TILs between the old and young patients to investigate potential age-related

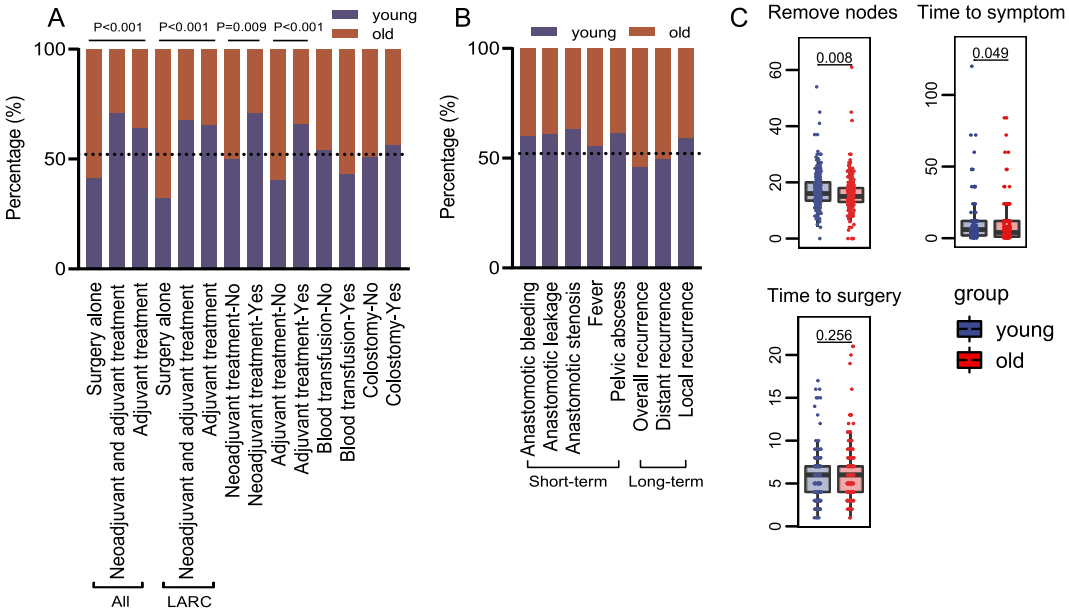

Fig. 2. Cancer care and treatment outcomes between two age groups (A) Cancer care in two age groups (Supplementary Tab. 6); (B) Short-term and long-term treatment outcomes between two age groups (Supplementary Tab. 7). (C) Number of lymph nodes removed, time from diagnosis to symptom onset (months), and time from admission to surgery (days) in two age groups (Supplementary Tab. 6). LARC, locally advanced rectal cancer.

differences in tumor characteristics and immune response that could impact prognosis and treatment decisions. Interestingly, we found that the two age groups were similar in molecular subtypes, including MMR status, CIMP status and mutations of *KRAS* and *BRAF* (Fig. 1B). In addition, the overall TIL counts (13.80 [11.23–18.27] vs. 14.70 [10.82–20.85] P = 0.188) and $CD8^+$ TIL counts (8.20 [2.00–26.00] vs. 15.20 [6.40–26.70], P = 0.170) were less in old patients, though the difference was not statistically significant (Fig. 1F).

3.3. Old age is associated with less cancer care

As shown in Fig. 2A, old patients received significantly less neoadjuvant (6.8% vs. 15.2%, P = 0.009) and adjuvant treatment (32.7% vs. 57.8%, P < 0.001) in the SYSU cohort. Specifically, the patients receiving neoadjuvant plus adjuvant treatment (7.1% vs. 15.6%) or adjuvant treatment alone (26.4% vs. 42.7%) were significantly less in old patients (P < 0.001). A similar finding was observed in the locally advanced rectal cancer (LARC) patients that needed to be given aggressive systemic treatment as recommended in the multiple guidelines (P < 0.001). Together, the old patients received less systemic treatment for rectal cancer compared with young patients.

To explore the role of old age as a potential cause for less systemic treatment, we used the multivariate logistic regression model to analyze the association of clinical features with absent systemic treatment. We found that old age, early T-stage, early N-stage and moderate/well tumor differentiation were independently associated with absent chemo/radiotherapy (Fig. 3). In the subgroup of stage III diseases, old age, early N-stage, and moderate/well tumor differentiation were independently associated with absent chemo/radiotherapy (Fig. 3).

Next, we evaluated the surgical treatment between the two age groups. The time from symptom onset to diagnosis in old patients was significantly longer than in young patients (median: 4 vs. 6 months, P = 0.049), suggesting the potential delayed diagnosis and treatment in the old patients (Fig. 2C). Of note, old patients had fewer lymph nodes removed than young patients (median: 15 vs. 16, P = 0.008, Fig. 2C), which is critical in the quality control of surgical resection for rectal cancer. However, our analysis showed that there were no significant differences in the incidence of common short-term postoperative complications, including fever, anastomotic bleeding, leakage, and stricture, as well as long-term recurrence, between the old and young patients (Fig. 2B). Taken together, we concluded that old age was associated with less cancer care in rectal cancer patients.

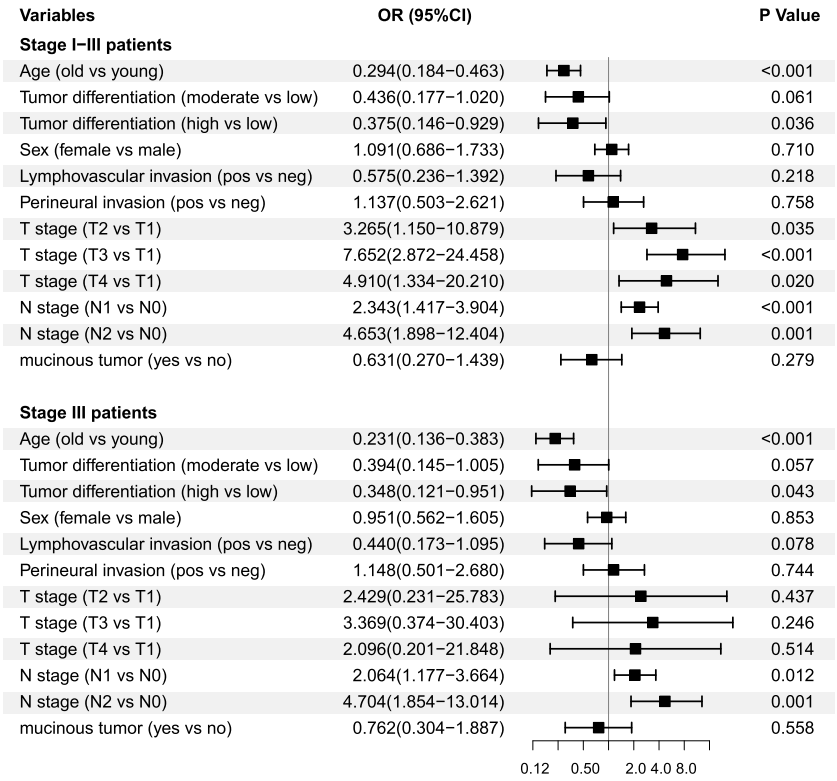

Fig. 3. Clinical features associated with less cancer care in old patients. Multivariate logistic regression analyses were conducted to analyze the association of age and clinical variables with absent systemic treatment for stage I-III and stage III rectal cancer patients, respectively. The association of each variable in the model was graphed as a forest plot. Data were presented as odds ratio (OR) with 95% confidential interval (CI).

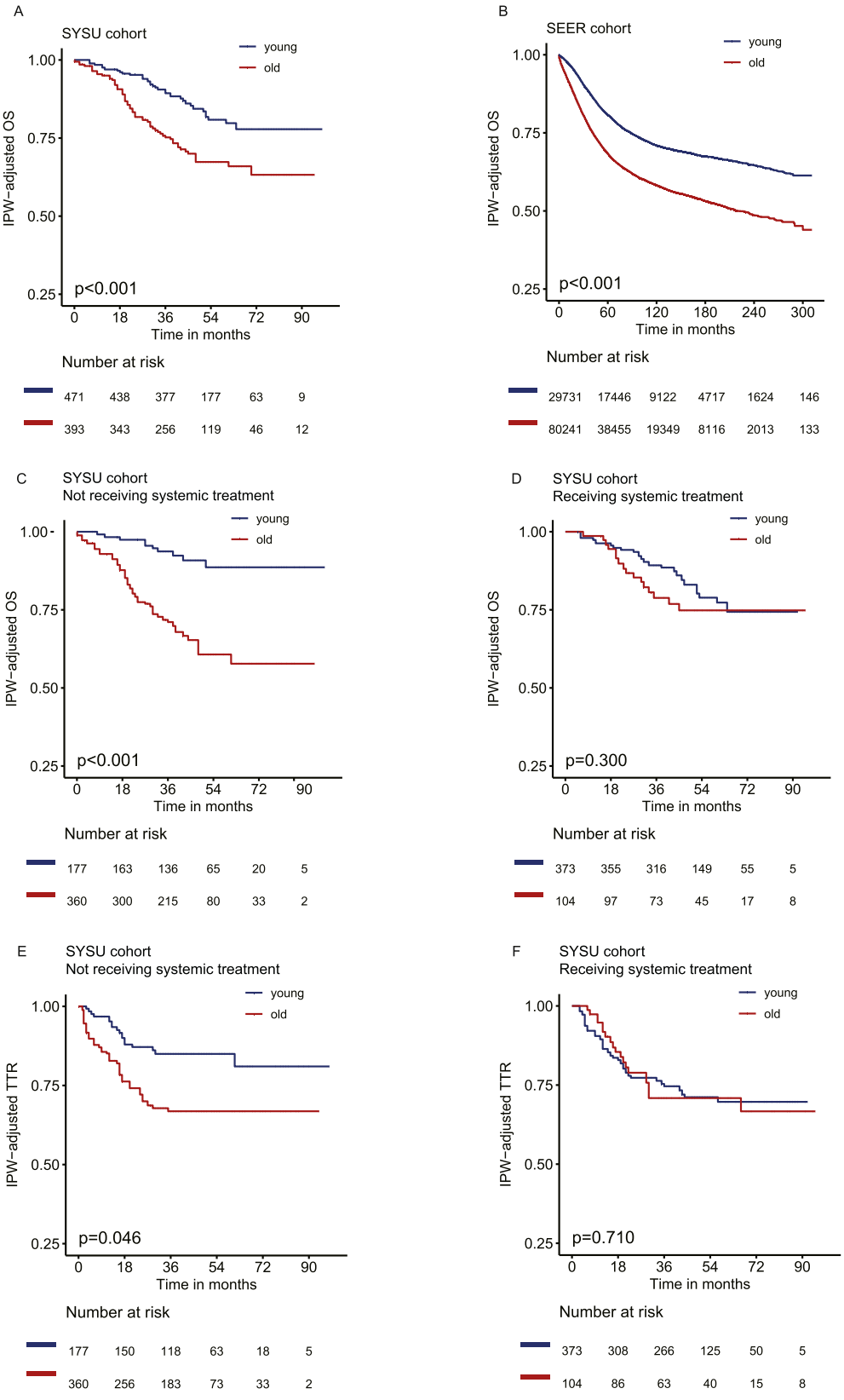

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Fig. 4. Survival outcomes of old and young patients with rectal cancer in two cohorts (A–B) IPW-adjusted OS curves showed that old patients had worse OS in the SYSU (A) and SEER (B) cohorts when compared with young patients. (C–D) IPW-adjusted OS curves in the subset of patients receiving (D) and not receiving (C) systemic treatment. (E–F) IPW-adjusted TTR curves in the subset of patients receiving (F) and not receiving (E) systemic treatment. The adjusted P value was given in each plot. OS, overall survival; TTR, time to recurrence.

3.4. Poor survival outcome in old patients is associated with insufficient systemic treatment

The incidences of overall, local and distant recurrences were similar between old and young patients (Fig. 2B), while the old patients had a significantly worse OS compared with young patients ($P < 0.001$, Figure S2A). This finding was validated in the SEER cohort ($P < 0.001$, Figure S2B). To eliminate the potential confounding impact of unbalanced clinicopathological risk factors, we applied the IPW-adjusted survival analysis to compare the two age groups and found that old patients had significantly worse OS outcomes in both SYSU ($P < 0.001$, Fig. 4A) and SEER ($P < 0.001$, Fig. 4B) cohorts.

To avoid the impact of chemo/radiotherapy on survival analysis, we performed the IPW-adjusted survival analysis in the subgroups stratified by treatment strategies. The significant prognostic value of old age in the subgroup not receiving chemo/radiotherapy ($P < 0.001$, Fig. 4C) turned to be insignificant in the subgroup receiving chemo/radiotherapy ($P = 0.300$, Fig. 4D). To avoid the confounding impact of non-cancer-cause death from aging, we further evaluated the TTR in each subgroup analysis. A similar reversion of the prognostic value of old age was observed in the patients receiving ($P = 0.046$, Fig. 4E) and not receiving ($P = 0.710$, Fig. 4F) chemo/radiotherapy.

4. Discussion

In this study, we generated a clinical atlas of old patients with rectal cancer by comprehensively comparing demographic and clinicopathological features, molecular profiles, treatment strategies, and clinical outcomes between the old and young patients. From the atlas, we found that old patients with rectal cancer were characterized by less cancer care, including delayed diagnosis and less systemic treatment. In addition, old patients had a higher incidence of hypertension and worse nutritional status. Importantly, old age was independently associated with absent chemo/radiotherapy. Old patients were similar to young patients in clinicopathological risk factors and tumor biology associated with survival outcomes. However, old age was independently associated with worse survival outcomes and less cancer treatment. In the subgroup analysis, the death and recurrence risk of old age in the subgroup not receiving chemo/radiotherapy reverted into no significant risk in the subgroup receiving chemo/radiotherapy. Based on these findings, we concluded that the insufficient cancer care for old age might contribute to the poor prognosis in old patients with rectal cancer.

In this study, we found that old age was an independent factor associated with a lack of systemic treatment. The age-related factors that may contribute to less cancer care for old patients include the physicians' concern for the safety of therapy, lack of physician counseling, patients' willingness, and the comorbidities, malnutrition, and frailty in old patients [38–41]. In our cohort analysis, we found that old rectal cancer patients have more comorbidities and worse nutritional status, which is consistent with previous findings [42–44]. An altered nutritional status has been recognized to be associated with an increased risk of toxicity after chemotherapy [45] and severe complications after surgery [46–48]. Moreover, some studies have reported that poor physical conditions or functional impairment from comorbidities may influence treatment decisions [49,50]. Together, this comprehensive understanding of the lack of treatment in old patients may provide additional insights into the strategies for geriatric assessment and intervention to include more old patients in the clinical trials and optimal cancer care pathways.

In the subgroup analysis, the survival outcome of old patients was significantly improved and was as good as young patients in the subgroup receiving chemo/radiotherapy, suggesting that systemic cancer treatment is effective and may be considered for the old patients. In addition, old patients showed a similar incidence of short-term postoperative complications and long-term recurrence to young patients. Therefore, surgical resection should be considered in old patients that are appropriate for the treatment.

Immunotherapy, such as immune checkpoint inhibitors (ICIs), has reshaped the treatment and outcome of patients with colorectal cancer [51,52]. It has been proposed that old age should not be considered a contraindication for immunotherapy. However, limited data regarding the efficacy and safety of novel checkpoint inhibitors in the old population because frail old patients are generally excluded from clinical trials [53,54]. Available evidence suggest that old patients can benefit from ICIs, and the safety and tolerability are good in this age group [55–57]. Moreover, we found that old patients presented with more dMMR tumors, which is a well-documented marker for a favorable response to immunotherapy [58], although it had no statistical significance. Therefore, age should not be considered an exclusion criterion in the clinical trials on immunotherapy, and the suitability for immunotherapy should be evaluated in the geriatric assessment.

Currently, few clinical trials focus on the old cancer patients [59–62], and the aging population in randomized clinical trials is still underrepresented due to adherence and toxicity concerns. Consequently, the efficacy and safety results from clinical studies could not adequately represent the old patients. Therefore, we proposed that the old population should be specifically considered in the trials on innovative therapies if a comprehensive geriatric assessment could be performed for the old patients, including functional status, comorbidities and physical status, mental and emotional status, social support, and economic status.

Our study has notable strengths. First, we focused on rectal cancer patients over 50 years, avoiding the confounding impact of early-onset cancers. Then, we used the IPW method and multivariate regression models adjusted by multiple clinicopathological risk factors, which may reduce the effect from unbalanced distribution of potential confounding factors between groups. However, our study was limited by its observational design, and well-designed clinical trials are requested to investigate the appropriate treatment regimens in

the optimal subgroup of old patients. Additionally, future data collection should consider including the proportion of preserved anus as an additional variable to provide a more comprehensive assessment of treatment outcomes.

5. Conclusion

Old patients with rectal cancer are characterized by more comorbidities, worse nutritional status, and less cancer care. Although old patients had similar tumor features compared to young patients, they had unfavorable survival outcomes associated with insufficient systemic treatment from old age. Moreover, the trials that included more old patients and the specific trials designed for old patients are needed to identify the optimal treatment regimens, test innovative therapeutics, and improve cancer care for old patients. Comprehensive geriatric assessment and intervention may help to include more old patients in the clinical trials and pathways with appropriate treatment regimens.

Ethical approval

The study protocol was reviewed and approved by the Institutional Review Board of the Sixth Affiliated Hospital of Sun Yat-sen University (No. 2017ZSLYEC-006).

Consent for publication

Written informed consent was obtained from all subjects or their representatives for the study participation.

Author contribution statement

Zhuoyang Zhao: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Huichuan Yu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Shunlun Chen; Heng Wang; Gaopo Xu; Zenghong Huang; Yingjie Li; Yu Zhang; Puning Wang: Performed the experiments; Wrote the paper.

Jinxin Lin; Xiaolin Wang: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Jianru Wang; Xiaoxia Liu; Meijin Huang; Yanxin Luo: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Ruwen Zhou: Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

The authors do not have permission to share data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15966.

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