Risk Analysis of Severe Thrombocytopenia in Nasopharyngeal Carcinoma During Concurrent Radio-Chemotherapy

Jiasheng Xu
the Second Affiliated Hospital of Nanchang University
Quanli Wu
Nanchang University
Luoyong Tang
the Second Affiliated Hospital of Nanchang University
Anwen Liu
the Second Affiliated Hospital of Nanchang University
Long Huang (huanglongncu@163.com)
the Second Affiliated Hospital of Nanchang University

Research Article

Keywords: nasopharyngeal carcinoma, platelet depletion, concurrent radio-chemotherapy, risk factors, predictive factors

Posted Date: May 25th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-386898/v1

Abstract

Objective: To explore the risk factors and predictive indexes of severe thrombocytopenia during concurrent radio-chemotherapy of nasopharyngeal carcinoma.

Methods: Retrospective analysis were performed from the hospitalized patients with nasopharyngeal carcinoma from August 2014 to July 2017 and completed induction chemotherapy and concurrent radio-chemotherapy.Patients were divided into observation and control group according to the lowest platelet count during concurrent chemotherapy. The general information and laboratory examinations were recorded and analyzed by univariate analysis, multivariate regression analysis and ROC curve analysis.

Results: Take the factors, including Age, PLT, IBIL, APTT at first visit, WBC, RBC, HGB, PLT, NEUT, APTT,IBIL, FFA, Crea,Urea before radio-chemotherapy, which are significant in univariate analysis into multivariate regression analysis. It turned out that RBC（OR=10.060, 95%CI2.679-37.777, P=0.001）,PLT(OR= 1.020, 95%CI1.006-1.034, P=0.005) and IBIL（OR=0.710,95%CI 0.561-0.898, P= 0.004） are independent predictors of severe TP in NPC. ROC analysis showed that the AUC of RBC, IBIL, PLT, AGE is 0.746(P< 0.001), 0.735（P<0.001）, 0.702(P=0.001), 0.734(P<0.001). New variables called joint predictor was calculated by regression equation (Y=2.309*RBC-0.343*IBIL+0.02*PLT-10.007), the AUC of which is 0.870(P<0.001), best truncation value is（5.87 mmol/L.

Conclusions: Lower RBC, PLT, higher IBIL before concurrent radio-chemotherapy are the independent risk factors causing severe TP during concurrent radio-chemotherapy of NPC. The RBC, PLT, IBIL before concurrent radio-chemotherapy and joint predictor have a good predictive value to evaluate the risk of severe TP during concurrent radio-chemotherapy of NPC.

Introduction

Nasopharyngeal carcinoma is a malignant tumor with high incidence and mortality rate in China, the morbidity and mortality rate of nasopharyngeal carcinoma in China are 0.019‰ and 0.012‰, which are considerably higher than that over the world[1-3]. Its pathogenesis is still unclear, which may relate to genetic factors, environment, infection of EB virus and so on[4,5]. In clinical cases, the proportion of patients in stage I, II, III, IV is separately 4.0%, 21.8%, 33.6%, 32.6%[6], most patients are in the late stage. Radiotherapy is the principle treatment for nasopharyngeal carcinoma with no distant metastasis. And it is reported that compared with simple radiotherapy, concurrent radio-chemotherapy can produce an increase of 4%-6% in 5-year overall survival and a decrease of 40%-52% in mortality risk in the patients in T3-4[6,7].

As National Comprehensive Cancer Network(NCCN) suggested, for the patient who are in T1,N1-3 and T2-T4, the therapeutic regimen includes sequential concurrent radio-chemotherapy after induction chemotherapy, and sequential concurrent radio-chemotherapy followed by adjuvant chemotherapy[8]. A meta analysis showed that comparing to simple concurrent radio-chemotherapy, applying induction

chemotherapy before concurrent radio-chemotherapy can significantly decrease the risk of local development and distal metastasis of nasopharyngeal carcinoma [9]. In our department, most patients have been treated with induction chemotherapy plus sequential concurrent radio-chemotherapy (usually Docetaxel and Platinum) for 3 periods.

Concurrent radio-chemotherapy can increase the survival rate, however, it is also accompanied by the increased risk of complications, some patients who received induction chemotherapy showed severe platelet depletion, which is a consequence of III~IV bone marrow suppression(BMS)[10], but the platelet count of some other patients appeared to be normal or slightly reduced. The reason of BMS is that chemotherapy can indiscriminately suppresses any cells which are actively growing[11], therefore, both tumor and non-tumor cells especially hematopoietic stem cells will be massively killed, leading to BMS. Chemo- and radiotherapy can be acceptable only when the platelet count≥$80*10^9$, when PLT≤$25*10^9$ which is caused by IV BMS, it can lead to spontaneous hemorrhage, chemo- and radiotherapy must be stopped or adjusted[12]. It is reported that the severe hemotoxic reaction is the main reason of radio-chemotherapy delay[13].

This research is aimed to explore the risk factors and predictive indexes of severe platelet depletion during concurrent radio-chemotherapy of nasopharyngeal carcinomas, therefore advanced interfere treatment can be available for those patients who might show severe platelet depletion during concurrent radio-chemotherapy. And there are no similar researches in this field, which brings great insight in the study of chemotherapeutics.

1. Methods

1.1 Research information

All the research objects are the patients from the Department of Oncology, the Second Affiliated Hospital of Nanchang University from August 2014 to July 2017, the information is collected by Electronic Medical Record(EMR), the selection criteria of these patients are: (1)Pathologically diagnosed as nasopharyngeal carcinoma; (2)Induction chemotherapy was performed before concurrent radio-chemotherapy; (3)The concurrent radio-chemotherapy was completed. And during concurrent radio-chemotherapy, the patients whose lowest PLT≤$50*10^9$ were placed into the observation group, and whose lowest PLT≥$100*10^9$ were placed into the control group. The exclusion criteria are: (1)Lack of hospitalizing data; (2)Incomplete medical records. Each 40 patients were selected into observation group and control group according to selection and exclusion criteria.

1.2 research method

The general information of patients were recorded in detail, including age, gender, height, weight, PS score, pathological diagnosis, TMN stage, clinical stages, plan and dosage of radiotherapy and chemotherapy, length of stay during concurrent radio-chemotherapy and so on. And the laboratory

examination at first visit and before radio-chemotherapy were also taken into record, including blood routine, coagulation function, D-dimer, liver function, kidney function, blood lipid, C reaction protein, EBV-DNA and so on. The information of observation and control group were organized and analyzed. Univariate and multivariate analysis were proceeded to explore the risk factors and independent predictive factors of severe thrombocytopenia during concurrent radio-chemotherapy, and by using ROC curve to select the optimal cutoff point and evaluate the predictive value of these risk factors and joint predictor.

1.3 Statistical analysis

Normality test was used to test continuous variables, the results were described by mean value ± standard deviation or median and quartile, then according to the results, T test or non-parametric test was proceeded. Classified variables were described by frequency and constituent ratio, and analyzed by chi-square test. ROC curve was used to evaluate the predictive value and optimal cutoff point of the predictors, which is suggested by AUC. The independent variables were taken in in binary logistic regression model according to their clinical significance and P<0.05 in univariate analysis. All the statistical analysis were accomplished by SPSS24 and Medcalc17.11.5, the significance is determined as P<0.05.

2. Results

2.1 General information

From August 2014 to July 2017, there are 282 hospitalized patients with nasopharyngeal carcinoma in the Department of Oncology, the Second Affiliated Hospital of Nanchang University, 25 of which occurred matastasis, 33 of which refused treatment, 224 of which received induction chemotherapy and concurrent radio-chemotherapy. Among these 224 patients, the lowest platelet count during concurrent chemotherapy were recorded, according to the selection criteria, 40 cases were included into observation group, and 40 control cases were randomly selected, 80 cases in total.

The general information of these patients are shown in Table 1, the age between 2 groups(53 vs 43, P<0.001) has a significant difference, age will be included into Logistic regression analysis because it is one of factors that affects the state of bone marrow. Comparing with the chemotherapy dosage between 2 groups, the dosage of Docetaxel has no significant difference (406.75 vs 411.50, P=0.260), the dosage of Platinum has significant difference (562.68 vs 643.50, P<0.001). It should be emphasized that the mean dosage of platinum in observation group is lower than that in the control group, this result indicates that the dosage of platinum is not the factor that causes the different PLT count between 2 groups. Gender, BMI, body surface area, clinical stage, PS scoring, dosage of radiotherapy between 2 groups have no significant difference(P>0.05). the baseline information of 2 groups is matched, which is comparable.

2.2 Comparison of the laboratory examinations at first visit and before radio-chemotherapy between 2 group

The indicators of blood routine analysis, coagulation function, liver function, kidney function, blood lipid level, creatine kinase at first visit and before radio-chemotherapy were compared. The data at first visit are showed in Table.2, the PLT(190.55 vs 244.5, P<0,001), APTT(28.79 vs 32.50, P=0,011), IBIL(8.78 vs 6.10, P=0.009) between observation and control groups showed significant differences (P<0.05), other laboratory results including CRP, WBC, showed no significant differences(P>0.05) . The comparing data before radio-chemotherapy are showed in Table.3, WBC(5.07 vs 9.61, P=0.014), RBC(3.57 vs 4.02, P<0.001), Hb(108.25 vs 116.63, P=0.029), PLT(150.15 vs 189.15, P<0.001), ANC(3.15 vs 7.23, P=0.018), APTT(27.21 vs 30.65, P=0.01), IBIL(7.25 vs 4.73, P<0.001), free fatty acid(0.35 vs 0.23, P=0.013), Creatine(82.53 vs 68.71, P=0.01), urea(5.91 vs 5.09, P=0.041) between 2 groups showed significant differences, other laboratory indicators showed no significant difference(P>0.05).

2.3 Univariate analysis

In order to explore the risk factor of severe thrombocytopenia during concurrent radio-chemotherapy of nasopharyngeal carcinomas, a binary logistic regression model was estabilished, the change(severe depletion or normal) of PLT count was considered as a dependent variable, and the general information, indicators of laboratory examinations at first visit and before radio-chemotherapy were considered as independent variable, the assignments of observation and control group were 0 and 1. As shown in Table 4, the univariate analysis found that age(OR=0.912, 95%CI0.865-0.963, P=0.001), PLT(OR=1.021, 95%CI 1.010-1.033, P<0.001), IBIL(OR=0.863, 95%CI 0.767-0.970, P=0.013) and APTT(OR=1.126, 95%CI 1.023-1.241, P=0.016) at first visit, WBC(OR=1.170,95%CI 1.014-1.350,P=0.032), RBC(OR=5.396,95%CI 1.970-14.782,P=0.001), Hb(OR=1.031,95%CI 1.002-1.060,P=0.034), PLT(OR=1.016,95%CI 1.006-1.027,P=0.003), ANC(OR=1.172, 95%CI1.0071.364, P=0.041),ATPP(OR=1.126,95%CI 1.023-1.241,P=0.016), IBIL(OR=0.740,95%CI 0.614-0.893,P=0.002), free fatty acid(OR=0.045,95%CI 0.030-0.628,P=0.021), Creatine(OR=0.970,95%CI 0.945-0.995,P=0.018) and urea(OR=0.751,95%CI 0.565-0.998, P=0.049) before radio-chemotherapy showed significant differences(P<0.05).

2.4 Multivariate analysis

The above results suggested that laboratory examinations before radio-chemotherapy are more significant and relative. Age and the significant factors before radio-chemotherapy were taken into binary logistic regression analysis model to proceed multivariate regression analysis. The final regression equation is Y=2.309*RBC – 0.343*IBIL + 0.02*PLT -10.007. As shown in Table 5, RBC□OR=10.060, 95%CI 2.679-37.777,P=0.001□, PLT(OR= 1.020,95%CI 1.006-1.034,P=0.005), IBIL(OR=0.710,95%CI 0.561-0.898,P=0.004) are the independent predictors in nasopharyngeal carcinoma during concurrent radio-chemotherapy, low RBC, PLT and high IBIL are the independent risk factors.

2.5 ROC curve analysis

In order to evaluate the predictive value of the predictors, the ROC curve(Fig. 1) was made by considering the significant factors in univariate analysis as the test variable, the AUC of these fators are shown in Table 6, the sensitivity, specificity and optimal cutoff point are shown in Table 7. Among these, the AUC

and optimal cutoff point of RBC are 0.746(P<0.001) and ≤3.82, with the sensitivity of 70% and specificity of 70%; the AUC and optimal cutoff point of IBIL are 0.735(P<0.001) and 5.87 mmol/L, with the sensitivity of 62.16% and specificity of 82.5%; the AUC and optimal cutoff point of PLT are 0.702(P=0.001) and ≤144*10^9/L, with the sensitivity of 57.5% and specificity of 82.5%; the AUC and optimal cutoff point of age are 0.734(P<0.001) and >48, with the sensitivity of 72.5% and specificity of 67.5%. We are attempting to evaluate the platelet change during radio-chemotherapy by applying combined diagnosis. As the independent predictors, RBC, PLT and IBIL of patients can be taken into the regression equation(Y=2.309*RBC – 0.343*IBIL + 0.02*PLT -10.007), Y is called joint predictor, its AUC and optimal cutoff point are is 0.870(P<0.001) and ≤0.38 with the sensitivity of 86.94% and specificity of 77.50%(Fig.2), it has a significant difference(P<0.05) comparing to single variable, which shows better diagnostic value.(Table 8, Fig.3)

3. Discussion

During clinical practice, the progress of concurrent chemotherapy and even the therapeutic effect are adversely affected due to severe thrombocytopenia. This research explored the risk factors and predictive indexes of severe platelet depletion during concurrent radio-chemotherapy of nasopharyngeal carcinomas. The results suggested that 17.9% of patients suffered severe thrombocytopenia during concurrent chemotherapy. This research made a comparison between patients with and without severe thrombocytopenia, and collected their basic clinical information, the laboratory examinations in first visit and before chemo-radiotherapy to make correlation analysis. The univariate analysis shows that there are statistical significant differences in age, PLT and APTT in first visit, and PLT, WBC, RBC, Hb, ANC, IBIL, APTT, FFA, urea, creatine before chemo-radiotherapy. The laboratory examinations before chemo-radiotherapy are closer in time to chemo-radiotherapy, which have higher significance and research value. Therefore, the results of laboratory examinations before chemo-radiotherapy and age were considered into multi-factor analysis, which shows that RBC, PLT and IBIL before radio-chemotherapy are independent risk factors. Then by using ROC regression analysis to evaluate their predictive value, and a new variable called joint predictor with fine reference value was figured out by placing these 3 factors into regression equation, whose sensibility and specificity are 86.49% and 77.5%. During clinical practice, whether patients will appear severe thrombocytopenia during concurrent radio-chemotherapy can be predicted by computing the combined predictive factor, and advanced intervention treatment can be conducted.

Thrombocytopenia is a common disease that can be caused by many reasons, including not only blood system diseases but also non-blood system diseases such as liver diseases, hyperspleenism, infection, rheumatic diseases, hypothyroidism, radiotherapy, medication and so on. In the department of oncology, the commonest reason that cause thrombocytopenia is chemo- and radiotherapy caused BMS, BMS is manifested as decreased peripheral RBC, WBC, PLT and so on, leading to anemia, hemorrhage and decreased immunity. It is reported that radiotherapy in lung and pelvic cavity can easily lead to BMS, because sternum and pelvis are the main part of hematopoiesis in adult. While nasopharyngeal

carcinoma belongs to the pate tumor, the extent of BMS is relatively lower. In addition, different kinds of chemotherapy drugs can have different effect on BMS. Paclitaxel, vinorelbine, topotecan, gemcitabine, anthracycline, carboplatin and methotrexate have relatively more severe suppression on bone marrow, while vincristine, pemetrexed, bleomycin, cisplatin and Asparaginase cause lesser suppression on bone marrow.

Bone marrow is the main hematopoietic organ in adult, including hematopoietic cells and hematopoietic microenvironment(HM), hematopoietic cells are composed of hematopoietic stem cells(HSCs), hematopoirtic progenitor cells(HPCs), and precursor cells. HSCs is the primitive hematopoietic cells which have strong self-renewal and self-replicated abilities and differentiate into HPCs. HPCs have a limited self-renewal ability, its proliferation and differentiation can meet the demand of normal hematopoiesis and tackle with hematopoietic crisis. During acute BMS, which is a common consequence of chemo-radiotherapy, HSCs differentiate into HPCs in order to maintain normal hematopoiesis, however, when HSCs are harmed by chemo-radiotherapy, a potent bone marrow damage is created. HM is the living environment of HSCs, but also the key link of hematopoietic regulation[14].

This research found that, by comparing observation group to control group, the RBC and PLT before chemo-radiotherapy are lower, which are the independent risk factors of thrombocytopenia during chemo-radiotherapy. BMS is a common adverse effect of chemotherapy, peripheral WBC, RBC and PLT count reflect the reserve function of hematopoiesis. The half-life of granulocytes, PLT and RBC are 6-8h, 5-7d and 120d, therefore the number of the 3 series decrease at different time, granulocytes decrease first, the decrease of RBC is generally not obvious[15]. After 3 periods of chemo-radiotherapy, the bone marrow of patients with nasopharyngeal carcinoma is in a suppressed status, the WBC count changes obviously, then the PLT count, and finally the RBC count. The RBC and PLT count before chemo-radiotherapy reflect the bone marrow suppressed status in patients, which is accordance with the research results.

The univariate analysis showed that there is a statistical difference in age between 2 groups, but multivariate analysis suggested that age is not an independent risk factor. Researches indicated that the hematopoietic hypofunction of bone marrow is positively related to aging[16–18], which is not accordance with the results, the possible reasons is that this research is a single–center, retrospective research, which has its limitation. Therefore, further introspective research with larger sample size should be followed up. In addition, as an independent predictive risk factor, there is little correlational research about IBIL, further research about IBIL is necessary.

Meanwhile, lower RBC,PLT and higher IBIL before radio-chemotherapy are the independent risk factors in severe thrombocytopenia during concurrent radio-chemotherapy. Therefore, whether patients will suffer severe thrombocytopenia during concurrent radio-chemotherapy can be predicted by examining RBC, PLT, IBIL and joint predictor before radio-chemotherapy. However, this research might exist some deficiencies, small sample size and single-center studies can lead to selection bias. different study centers may have different definition of severe thrombocytopenia, and the discrepancy among different detecting instruments may lead to different results. Finally, this research is a retrospective analysis, which needs

prospective studies to further confirm, and severe thrombocytopenia may also exist in other kinds of tumor therapy, broader and further studies are still waiting to be proceeded.

Declarations

Funding: Not applicable.

Competing interests:Authors declare there are no conflicts of interest.

Availability of data and material: Not applicable.

Consent to participate: Informed consent was obtained from all subjects.

Ethics declarations: All experimental protocols were approved by the Department of Oncology, the Second Affiliated Hospital of Nanchang University. All methods were performed in accordance with the relevant guidelines and regulations.

Code availability: Not applicable.

Author contributions:

Author：JX& QW Contribution：

1：Design research direction 2：Writing papers

Author：LT & A L Contribution：

1：searching for references 2：helping to write papers

Author：LH Contribution：

1：Review and revise the papers 2：Guidance article writing

Acknowledgements：

*Jiasheng Xu and Quanli Wu are co-first authors of this article. Jiasheng Xu is the first of co-first authors,and Quanli Wu is the second of the co-first authors.

Data availability:

All data is available, please contact if necessary.

Consent to participate/Consent to publish: Informed consent was obtained from all subjects.

Ethics declarations: All experimental protocols were approved by the Department of Oncology, the Second Affiliated Hospital of Nanchang University. All methods were performed in accordance with the relevant

guidelines and regulations.

References

1. Chen W，Zheng R，Zhang S，et al. Report of incidence andmortality in China cancer registries，2009 [J]. ChineseJournal of Cancer Research，2013，25(1)，10.
2. Chen W，R Zheng，S Zhang，et al. Report of cancer inci-dence and mortality in China，2010 [J]. Ann Transl Med，2014，2(7)，61.
3. Chen WQ，Zheng RS，Zhang SW，et al. Report of cancerincidence and mortality in China，2012[J]. China Cancer，2016，25(1)，1-8.
4. Chang ET，Adami HO. The enigmatic epidemiology of na-sopharyngeal carcinoma[J]. Cancer Epidemiology Biomark-ers & Prevention，2006，15(10)，1765-1777.
5. Shang XL，Xie ZQ，Huang ZB. Risk factors for nasopha-ryngeal carcinoma [J]. Modern Preventive Medicine，2008，35(2)，206-207.
6. Deng W, Huang TR, Chen WQ, et al. Analysis of the incidenceand mortality of nasopharyngeal carcinoma in Chinabetween 2003 and 2007 [J]. Tumor, 2012, 32(3): 189-193.
7. Langendijk JA， Leemans CR， Buter J， et al， Theadditional value of chemotherapy to radiotherapy inlocally advanced nasopharyngeal carcinoma， a metaanalysisof the published literature [J]. J Clin Oncol，2004，22，22，，4604，4612，
8. Pfister DG，Spencer S，Brizel DM，et al， Head and Neck Cancers，Version 1，2015 [J]. J Natl Compr Canc Netw，2015，13:847，855，
9. Song Y，Wang W，Tao G，et al， Survival benefit of induction chemotherapy in treatment for locally advanced nasopharyngeal carcinoma—A time，to，event Meta - analysis [J]. Oral Oncol，2015，51:764，769，
10. Kuter DJ.General aspects of thrombocytopenia,platelet transfusions,and thrombopoietic growth factors.In: Kitchens C, Kessler C, Konkle B, editors.Consultative Hemostasis and Th rombosis .Philadelphia: Elsevier Saunders: 2013. p. 103-16.
11. Dimou M, Angelopoulou MK, Pangalis GA, e t al.Autoimmune hemolytic anemia and autoimmune thrombocytopenia at diagnosis and during follow-up of Hodgkin lymphoma. Leuk Lymphoma. 2012;53:1481-7.
12. Sun Y, Shi KY. *Manual of Medical Oncology,6th Edition.*People's Medical Publishing House,2015
13. Cho N, Nguyen DH, Satkunendrarajah K, et al. Evaluating the role of IL-11, a novel cytokine in the IL-6 family, in a mouse model of spinal cord injury[J]. J Neuroinflammation, 2012, 20(9): 134.
14. Muguruma Y,Yahata T,Miyatake H,et al.Reconstitutio functional human hematopoietic microenvironment derived from human mesenchymal stem cells in the murine bone marrow compartmen.Blood,2006,107(5):1878-18.
15. Sun Y, Shi KY. *Manual of Medical Oncology,6th Edition*, People's Medical Publishing House, 2015. P96

16. Geiger H1, Denkinger M2, Schirmbeck R3.Hematopoietic stem cell aging.Curr Opin Immunol. 2014 Aug;29:86-92. doi: 10.1016/j.coi.2014.05.002. Epub 2014 Jun 3.
17. Snoeck HW.Aging of the hematopoietic system.Curr Opin Hematol.2013 Jul;20(4):355-61. doi: 10.1097/MOH.0b013e3283623c77.
18. Larisa V,Kovtonyuk,Kristin Fritsch,Xiaomin Feng, Markus G. Manz,and Hitoshi Takizawa,Inflamm-Aging of Hematopoiesis, Hematopoietic Stem Cells, and the Bone Marrow Microenvironment.Front Immunol. 2016; 7: 502.

Tables

Table 1. General information

	Total（N=80）	Observation group （n=40）	Control group（n=40）	*P* value
Age(yrs)	**49(16-68)**	**53(37-68)**	**43(16-66)**	**0.001**
Gender				0.323
Male	56(70.0%)	31(77.5%)	26(65.0%)	
Female	23(30.0%)	9 (22.5%)	14(35.0%)	
BMI (kg/m2)	23.44±3.87	23.26±3.52	23.61±4.22	0.693
Body surface area（m^2）	1.66±0.16	1.68±0.18	1.64±0.15	0.262
Clinical stage				0.320
Ⅱ-Ⅲ	4	0	4	
Ⅲ-Ⅳ	76	40	36	
ECOG PS				0.723
0	28(35.0%)	15(37.5%)	13(32.5)	
1	44(55.0%)	23(57.5%)	22(52.5%)	
2	8(10.0%)	3 (5.0%)	5 (12.5)	
Platinum(mg)	**603.09±69.21**	**562.68±72.76**	**643.50±32.55**	**0.001**
Docetaxel(mg)	406.75±37.38	402.00±36.18	411.50±38.40	0.260
GTVnx（Gy）	70.60（70.00-72.2）	71.20（70.00-72.2）	70.00（70.00-72.20）	0741
GTVnd（Gy）	66.55（66.00-68.00）	67.10（66.00-68.00）	66.00 (66.00-68.00)	0..870
CTV1（Gy）	64.55（64.00-65.80）	65.10（64.00-65.80）	64.00（64.00-65.80）	0.784
CTV2（Gy）	54.95（54.40-56.20）	55.50（54.40-56.20）	54.40（54.40-56.20）	0.855

Table 2. Laboratory examination at first visit

Laboratory examination	Mean ± Standard deviation		*P* value
	Observation group	Control group	
CRP（mg/L）	3.62±3.37	6.03±6.68	0.064
WBC（10^9/L）	6.15±1.71	6.85±2.53	0.150
RBC（10^9/L）	4.48±0.5	4.59±0.54	0.345
Hemoglobin（g/L）	133.98±13.85	131.53±18.94	0.511
PLT（10^9/L）	**190.55±39.37**	**244.75±61.81**	**<0.001**
NEU(%)	65.84±8.95	63.83±13.18	0.428
LY(%)	25.82±6.99	25.32±8.5	0.778
MO(%)	6.76±3.44	6.46±2.93	0.681
EO(%)	1.55±1.64	2.45±2.76	0.083
BASO(%)	0.09±0.18	0.09±0.14	1.000
ANC(%)	4.01±1.55	4.33±1.91	0.409
Fibrinogen level(g/L)	2.90±0.95	3.22±0.97	0.154
PT(s)	11.83±2.28	11.47±1.72	0.431
INR	1.00±0.20	0.96±0.14	0.291
PTA(%)	103.91±21.92	112.96±31.99	0.145
APTT(s)	**28.79±4.68**	**32.50±7.69**	**0.011**
TT(s)	18.19±2.48	17.99±4.10	0.795
D-dimer(μmol/L)	0.98±0.88	1.31±2.07	0.363
Total protein（g/L）	70.72±8.58	69.00±5.41	0.290
Albumin（g/L）	41.32±3.92	41.25±2.73	0.923
Globulin（g/L）	29.39±5.6	27.75±3.9	0.134
DBIL(mmol/L)	3.39±1.62	3.90±1.90	0.210
IBIL(mmol/L)	**8.78±5.20**	**6.10±3.51**	**0.009**
ALT(U/L)	23.01±12.52	23.74±10.78	0.783
AST(U/L)	30.66±35.09	21.92±5.3	0.123

Laboratory examination	Mean ± Standard deviation		*P* value
	Observation group	Control group	
ALP(U/L)	88.32±2.05	96.49±31.7	0.188
GGT(U/L)	36.49±40.65	31.61±18.02	0.490
CHE(U/L)	7342.16±1903.64	10914.17±16897.63	0.247
TG(mmol/L)	1.25±0.62	1.47±0.82	0.245
PAB（mg/L）	230.82±80.15	236.76±7.88	0.730
TC(mmol/L)	4.36±0.81	4.49±1.09	0.592
FFA(mmol/L)	0.37±0.22	0.37±0.23	0.933
LDL(mmol/L)	2.54±0.71	2.55±0.74	0.968
HDL(mmol/L)	1.19±0.25	1.21±0.28	0.827
LDH(U/L)	182.87±63.78	172.47±40.10	0.449

Table 3. Laboratory examination before radio-chemotherapy

Laboratory examination	Mean ± Standard deviation		*P* value
	Observation group	Control Group	
CRP（mg/L）	3.62±3.98	3.48±3.48	0.881
WBC（10^9/L）	**5.07±2.22**	**9.61±11.02**	**0.014**
RBC（10^9/L）	**3.57±0.54**	**4.02±0.50**	**＜0.001**
Hemoglobin（g/L）	**108.25±15.89**	**116.63±17.80**	**0.029**
PLT（10^9/L）	**150.15±47.79**	**189.15±54.67**	**＜0.001**
NEU(%)	59.51±13.52	63.56±11.68	0.220
LY(%)	30.61±12.84	26.47±13.08	0.157
MO(%)	7.83±4.90	7.67±4.07	0.876
EO(%)	2.01±3.52	2.15±2.50	0.841
BASO(%)	0.038±0.11	0.14±0.38	0.098
ANC（10^9/L）	**3.15±1.95**	**7.23±10.48**	**0.018**
Fibrinogen level (g/L)	3.10±0.88	2.99±0.9	0.628
PT(s)	11.33±1.20	11.44±1.2	0.698
APTT(s)	**27.21±5.15**	**30.65±5.98**	**0.010**
TT(s)	17.91±1.78	18.82±4.37	0.254
D-dimer(μmol/L)	1.25±0.74	1.18±0.52	0.633
Total protein（g/L）	65.55±7.84	66.19±4.99	0.666
Albumin（g/L）	39.76±4.10	40.62±2.8	0.285
Globulin（g/L）	26.33±4.50	25.58±3.12	0.394
DBIL(mmol/L)	2.85±1.55	3.01±1.41	0.631
IBIL(mmol/L)	**7.25±3.23**	**4.73±2.77**	**＜0.001**
ALT(U/L)	19.63±9.91	25.21±14.62	0.056
AST(U/L)	22.67±6.57	23.70±6.79	0.502
ALP(U/L)	84.34±25.29	92.42±25.69	0.169
GGT(U/L)	35.03±27.93	37.85±28.92	0.665
CHE(U/L)	7073.73±1766.04	7836.21±1301.36	0.075

Laboratory examination	Mean ± Standard deviation		*P* value
	Observation group	Control Group	
TG(mmol/L)	1.78±1.16	345.38±1850.5	0.349
PAB（mg/L）	246.67±1.40	243.91±67.11	0.866
TC(mmol/L)	4.86±0.93	4.75±0.99	0.685
FFA(mmol/L)	**0.35±0.26**	**0.23±0.14**	**0.013**
LDL(mmol/L)	2.91±0.8	2.69±0.73	0.292
HDL(mmol/L)	1.170.33	1.17±0.32	0.979
CK(U/L)	68.97±36.25	73.72±9.13	0.594
CK-MB(U/L)	9.83±2.76	9.56±4.14	0.778
LDH(U/L)	158.02±28.61	160.54±28.64	0.746
Creatine(μmol/L)	**82.53±27.24**	**68.71±7.95**	**0.010**
UA(μmol/L)	353.86±79.7	326.33±91.75	0.166
Urea(mmol/L)	**5.91±1.67**	**5.09±1.77**	**0.041**
SOD(U/L)	162.18±27.24	164.15±28.77	0.767

Table 4. Univariate analysis

Variate	OR value（95%CI）	*P* value
Age	0.912（0.865-0.963）	0.001
PLT at first visit	1.021（1.010-1.033）	＜0.001
APTT at first visit	1.126（1.023-1.241）	0.016
IBIL at first visit	0.863（0.767-0.970	0.013
WBC	1.170（1.014-1.350）	0.032
RBC	5.396（1.970-14.782）	0.001
Hemoglobin	1.031（1.002-1.060）	0.034
PLT	1.016（1.006-1.027）	0.003
ANC	1.172（1.007-1.364）	0.041
APTT	1.126（1.023-1.241）	0.016
IBIL	0.740（0.614-0.893）	0.002
FAA	0.045（0.030-0.628）	0.021
Creatine	0.970（0.945-0.995）	0.018
Urea	0.751（0.565-0.998）	0.049

Table 5. Multivariate analysis

	B	Standard error	Ward	DOF	Significance	OR	OR95% CI	
							Lower limit	Upper limit
RBC	2.309	0.675	11.695	1	0.001	10.060	2.679	37.777
PLT	0.020	0.007	8.033	1	0.005	1.020	1.006	1.034
IBIL	-0.343	0.120	8.179	1	0.004	0.710	0.561	0.898
Constant	-10.007	3.101	10.413	1	0.001	0.000		

Table 6. AUC of each test variable

Test variable	AUC	SD	95% CI	*P* value
Joint predictor	0.877	0.0484	0.780 to 0.942	<0.001
RBC	0.746	0.057	0.631 to 0.840	<0.001
IBIL	0.735	0.0584	0.620 to 0.831	<0.001
Age	0.734	0.058	0.621 to 0.847	<0.001
PLT	0.702	0.0605	0.585 to 0.803	0.001
APTT	0.679	0.062	0.561 to 0.783	0.008
Urea	0.663	0.0634	0.543 to 0.769	0.020
Creatine	0.660	0.063	0.537 to 0.784	0.015
Hemoglobin	0.643	0.063	0.520 to 0.766	0.028
FAA	0.638	0.064	0.512 to 0.763	0.038
WBC	0.634	0.063	0.510 to 0.758	0.039
ANC	0.600	0.065	0.473 to 0.727	0.122
NEU	0.553	0.066	0.424 to 0.681	0.419

Table 7. Predictive value of each test variable

Test variable	AUC	Sensitivity	Specificity	Optimal cutoff point
Joint predictor	0.877	86.49	77.50	≤0.38
RBC	0.746	70.00	70.00	≤3.82
IBIL	0.735	62.16	82.50	≥5.87
Age	0.734	77.50	67.50	≥47
PLT	0.708	57.50	82.50	≤144
APTT	0.679	61.11	76.32	≤26.9
Urea	0.663	67.57	60.00	≥5.09
Creatine	0.660	48.65	82.50	≥80.4
Hemoglobin	0.643	82.50	50.00	≤117
FFA	0.638	70.27	55.00	≥0.21
WBC	0.634	85.00	42.50	≤6.43
ANC	0.600	92.50	35.00	≤5.24
NEU	0.553	90.00	35.00	≤73.9

Table 8. Comparison of predictive value between Joint predictor and single variable

	Value of area difference	SD	95%CI	Z-statistic	Level of significance
Joint predictor vs RBC	0.131	0.055	0.023-0.239	2.376	0.018
Joint predictor vs PLT	0.175	0.061	0.055-0.295	2.868	0.004
Joint predictor vs IBIL	0.142	0.053	0.038-0.246	2.677	0.007
Joint predictor vs Age	0.144	0.066	0.016-0.273	2.201	0.028
Joint predictor vs APTT	0.198	0.072	0.057-0.338	2.760	0.006

Figures

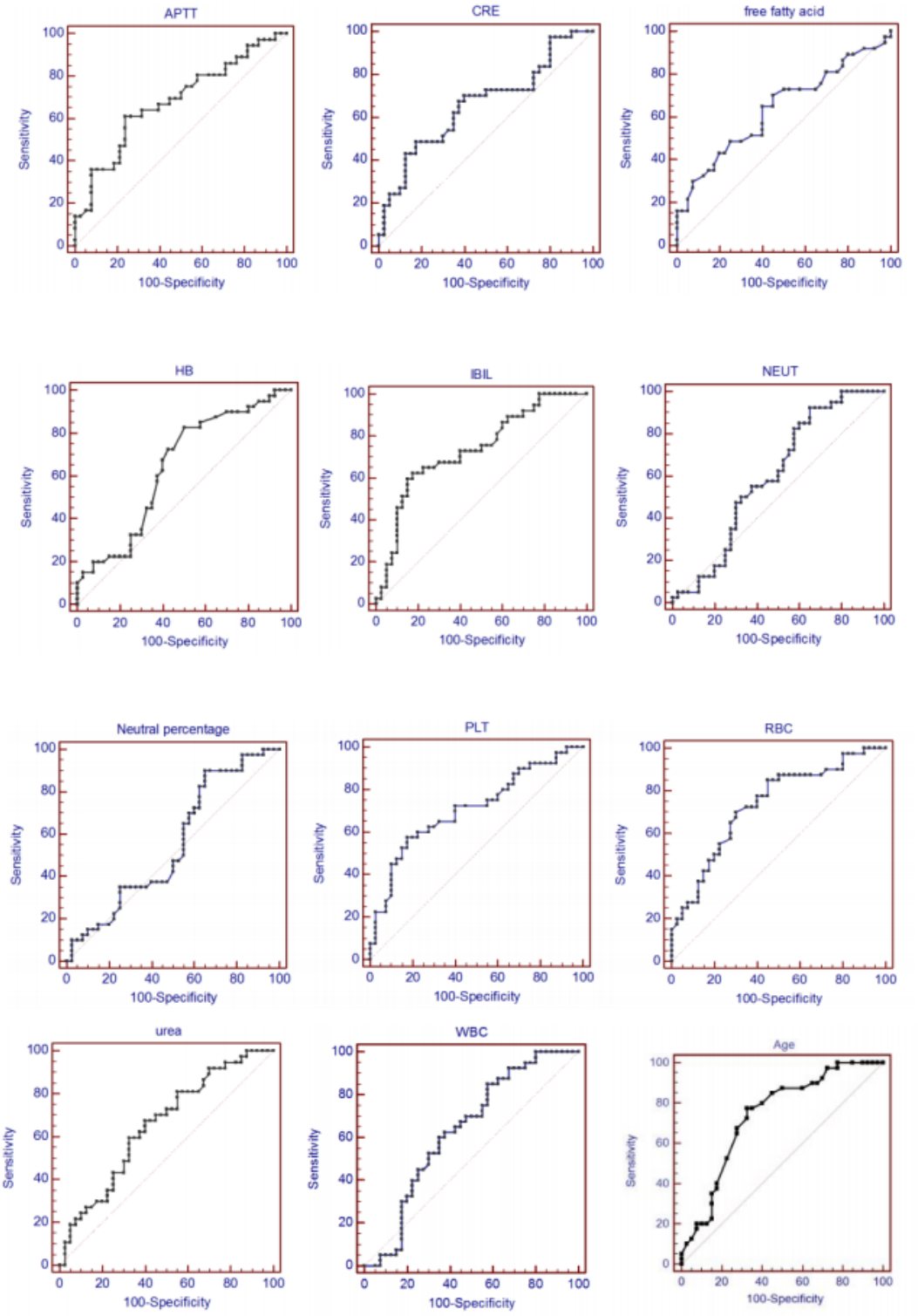

Figure 1

ROC curve of each test variable

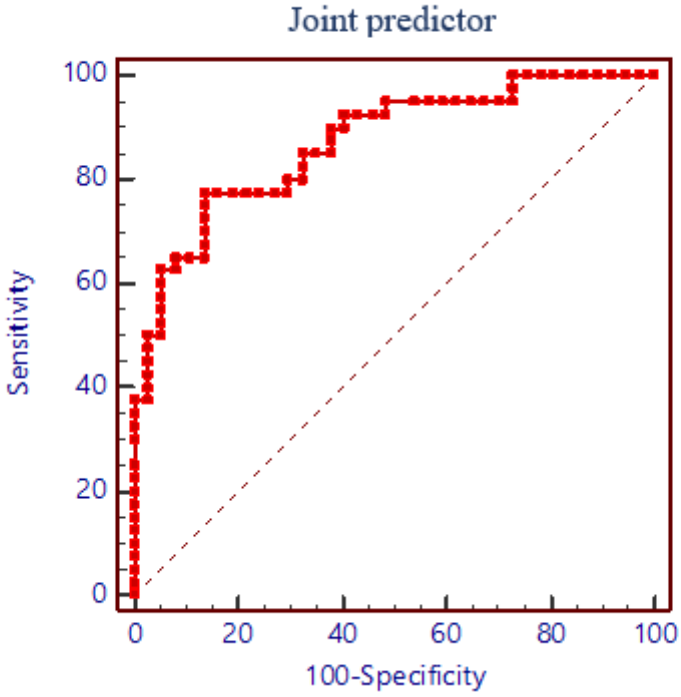

Figure 2

ROC curve of joint predictor

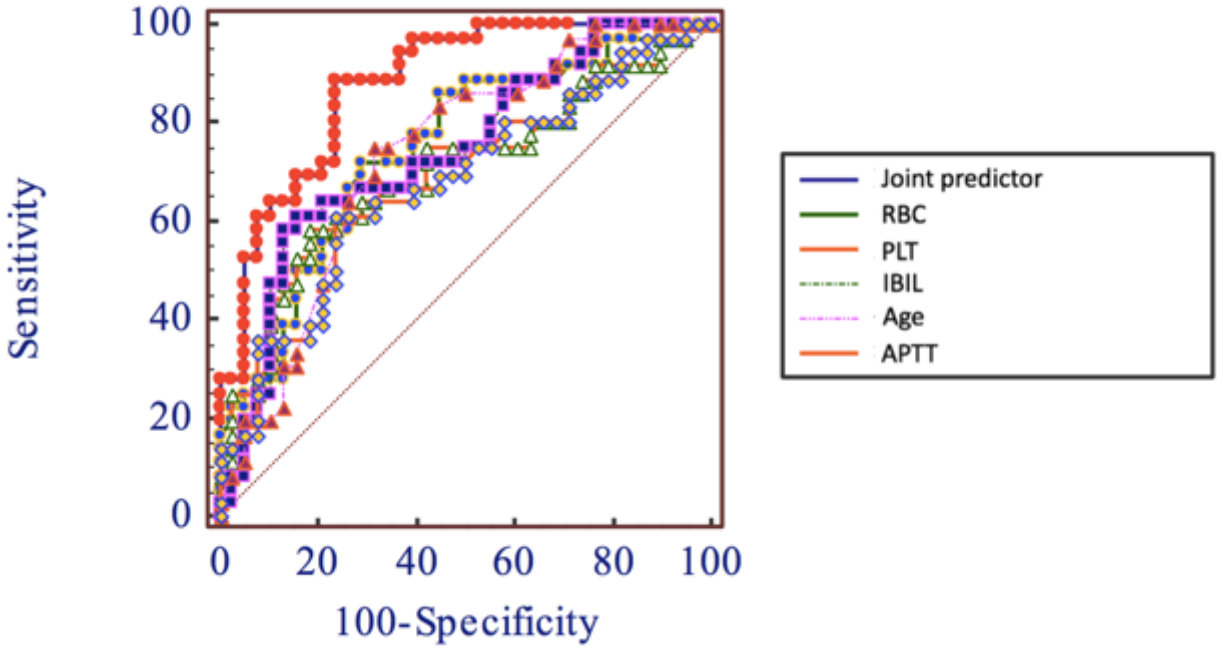

Figure 3

Comparison between joint predictor and other single factor