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Routine coagulation molecules predict nasopharyngeal carcinoma and associated metastases

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ABSTRACT

Introduction: Most patients with malignant solid tumours have abnormal blood coagulation and an abnormal peripheral blood count, but data on nasopharyngeal carcinoma is scare. We hypothesised abnormal coagulation indices and red cell distribution width (RDW) in this group that are linked to the tumour (T), lymph node (N) and metastatic aspects (M) of the patients.

Methods: We recruited 740 newly diagnosed patients with nasopharyngeal carcinoma and 238 healthy controls, taking venous blood for prothrombin time, activated partial thromboplastin time (APTT), thrombin time, fibrinogen, fibrin degradation products (FDP), D-dimer, RD), platelets and platelet distribution width (PDW). In the patients, lab indices were analysed according to clinical stage.

Results: All indices except thrombin time were significantly different between cases and controls ($p < 0.001$), and many predicted TNM classifications and early or late stage of the disease. In sensitivity/specificity analysis, the prothrombin time, APTT and PDW gave AUCs >0.7, and in combination gave an AUC of 0.88 (95% CI 0.86–0.91) for nasopharyngeal carcinoma. No index provided an AUC >0.7 for T or N classification, or early v late stage, but APTT, fibrinogen and FDP all gave AUCs ≥0.7 for predicting metastases. Together, these three indices gave an AUC of 0.84 (0.78–0.91).

Conclusions: Routine coagulation indices can predict nasopharyngeal carcinoma, with the combination of prothrombin time, APTT and PDW being strongest. The combination of APTT, fibrinogen and FDPs provides a useful score to predict metastases. These indices should be considered in the diagnosis and staging of this disease.

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KEYWORDS
Nasopharyngeal carcinoma; coagulation function; blood cell count

Introduction

Nasopharyngeal carcinoma is a common malignant tumour in otorhinolaryngology, linked to around 80,000 new cases each year and 50,000 deaths a year globally [1]. Incidence varies with geography, occurring at a frequency of around 80/100,000 in South East Asia to less than 1/100,000 in the West [2]. The disease may be categorised into non-keratinised squamous cell carcinoma, squamous cell carcinoma and basal cell-like squamous cell carcinoma. The aetiology is still unclear, but some studies indicate that it may be related to Epstein-Barr virus infection, environment, and heredity. Early diagnosis of nasopharyngeal carcinoma is difficult and 60–70% of presentations are at a late stage. The 5-year survival rate of stage 0 is close to 100%, falling to 80% for stage 1, 60% for stage 2, 30–40% for patients stages III, IVa and IVb, and <10% in patients with distant metastatic disease (IVc). However, radiotherapy combined with chemotherapy is improving outcomes: in stage III patients having a combination of chemo- and radiotherapy, the 3-year survival rate has increased by 30% compared with radiotherapy alone [1,3].

Accordingly, tools to improve the diagnosis and management of nasopharyngeal carcinoma are called for. It has long been known that cancer is a pro-coagulant state [4]: haemostasis is not simply involved in the mechanism of haemostasis, but also in the process of tumour metastasis, which creates a condition for the invasion and metastasis of malignant tissues [5]. Using a proteomic approach, Peng et al. identified abnormalities in several coagulation-related molecules in nasopharyngeal carcinoma, but failed to report relationships with clinical indices [6]. Therefore, we hypothesised abnormalities in routine and accessible markers of haemostasis that are linked to clinical features and to prognosis.

Materials and methods

All specimens were taken from subjects referred to the people's Hospital of Guangxi Zhuang Autonomous region. All patients were diagnosed between January 2013 and May 2018, and were untreated: the diagnosis was confirmed by histopathology. Patients were classified by the TNM (tumour, lymph nodes, metastases) American Joint Committee of Cancer

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clinical staging algorithm as modified by the 2008 revision of the Chinese mainland staging system [1]. According to the clinical TMN stage and 5-year survival rate >60%, we preliminarily defined stage I, II as an early group and stage III, IV as a late group. The control group was randomly selected healthy subjects presenting for physical examination. Exclusion criteria for all subjects were hematologic diseases, deep venous thrombosis, major surgery, other tumours, and diseases affecting coagulation and blood cell counts. No drugs had been taken for the last three months that affect coagulation function and blood cell count. The study was conducted in accordance with good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the ethics committee of the People's Hospital of Guangxi Zhuang Autonomous Region. All patients were informed and agreed to participate in the study.

Venous blood was taken into 109 mmol/L sodium citrate or EDTA. After 3000 r/min centrifugation of the former for 10 min, plasma was tested for prothrombin and thrombin times, APTT, fibrinogen, fibrin degradation products (FDP) and d-dimers (STA-R Evolution, Stago, France) within 2 h. Red cell distribution width (RDW), platelet count, and platelet distribution width were determined in the EDTA sample within 2 h (XE-2100, XN-9000, Sysmex, Japan). Data was analyzed by statistical SPSS 18.0 software. Groups were compared by t-test. Receiver operator characteristic curve and area under the curve (AUC, with a 95% confidence interval) were used to judge the sensitivity and specificity. In view of our large sample size (case/control $n = 978$, cases $n = 740$), and multiple and inter-related indices, we took $p \leq 0.01$ to be significant to minimise the risk of false positives.

Results

The 740 patients with nasopharyngeal carcinoma were 539 males and 201 females, the 238 controls were 153 males and 85 females ($p = 0.012$). The cases had a mean [SD] age of 47.1 [11.5] years, the controls were aged 47.0 [10.0] years ($p = 0.663$). Comparison of blood parameters between cases and controls is shown in Table 1. All except thrombin time were significantly different between the two groups. The APTT, fibrinogen and platelet count predicted T classification, fibrinogen predicted N classification, the APTT and fibrinogen predicted metastases and the fibrinogen and platelet count predicted early versus late stage.

Table 2 shows an area under the curve analyses. All indices except thrombin time predicted nasopharyngeal carcinoma. Prothrombin time (cut-off 12.75 s, sensitivity 0.72, specificity 0.63), the APTT (cut-off 35.55 s, sensitivity 0.66, specificity 0.75) and the PDW (cut-off 12.95, sensitivity 0.57, specificity 0.89) all gave superior AUCs of >0.7. Accordingly, these were combined, and this score provided a higher AUC with a sensitivity of 0.98 and a specificity of 0.35 for the detection of nasopharyngeal carcinoma. Although the APTT, fibrinogen and the platelet count predicted T classification, and fibrinogen and platelet count predicted N classification, AUCs were modest (<0.7). However, the APTT (cut-off 38.25 s, sensitivity 0.71, specificity 0.65), fibrinogen (cut-off 3.12, sensitivity 1.00, specificity 0.37) and FDPs (cut-off 1.55, sensitivity 0.83, specificity 0.52) all gave AUCs ≥0.7. Similarly, these were combined into a score for the prediction of metastases, which gave a superior AUC than each index alone, with a sensitivity of 1.00 and a specificity of 0.14. AUCs for indices prediction early versus late stage were modest (AUC < 0.7). Figures 1 and 2 show AUC plots for indices predicting the cancer, and for predicting metastases.

Discussion

The link between thrombosis was described in detail by Trousseau in 1865, and is now widely established. Malignant tumour cells cause changes in blood

Table 1. Main clinical characteristics of patients group according to laboratory data.

		Coagulation Parameters								
Variables	N	PT (sec)	APTT (sec)	Thrombin time (sec)	FIB (g/L)	FDP (ug/ml)	D-D (mg/L)	RDW (%)	Platelet Count (10^9/L)	PDW (%)
Nasopharyngeal carcinoma										
Cases	740	13.3 ± 0.7	37.6 ± 4.2	16.9 ± 1.2	3.6 ± 1.0	1.7 ± 1.1	0.58 ± 0.50	13.5 ± 1.4	268 ± 67	11.2 ± 1.7
Controls	238	12.6 ± 0.6	33.9 ± 2.7	16.8 ± 0.7	3.1 ± 0.5	1.3 ± 0.6	0.31 ± 0.12	12.7 ± 0.8	248 ± 53	13.6 ± 2.5
		$p < 0.001$	$p < 0.001$	$p = 0.016$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
T classification										
T1-2	293	13.2 ± 0.7	36.8 ± 3.8	17.0 ± 1.1	3.3 ± 1.0	1.7 ± 1.2	0.52 ± 0.40	13.3 ± 1.2	259 ± 56	11.3 ± 1.6
T3-4	447	13.2 ± 0.7	37.7 ± 4.1	16.9 ± 1.2	3.8 ± 1.0	1.9 ± 1.5	0.54 ± 0.54	13.4 ± 1.2	279 ± 70	11.1 ± 1.7
		$p = 0.222$	$p = 0.004$	$p = 0.317$	$p < 0.001$	$p = 0.228$	$p = 0.528$	$p = 0.458$	$p < 0.001$	$p = 0.134$
N classification										
N0-1	258	13.2 ± 0.7	37.6 ± 4.5	17.1 ± 1.3	3.5 ± 1.0	1.9 ± 1.4	0.55 ± 0.55	13.4 ± 1.2	264 ± 61	11.2 ± 1.6
N2-3	482	13.2 ± 0.7	37.2 ± 3.8	16.9 ± 1.1	3.7 ± 1.1	1.8 ± 1.4	0.52 ± 0.45	13.3 ± 1.2	275 ± 68	11.2 ± 1.7
		$p = 0.730$	$p = 0.252$	$p = 0.146$	$p = 0.010$	$p = 0.658$	$p = 0.439$	$p = 0.445$	$p = 0.024$	$p = 0.968$
M classification										
Metastasis absent	716	13.2 ± 0.7	37.2 ± 4.0	17.0 ± 1.2	3.6 ± 1.0	1.8 ± 1.3	0.52 ± 0.46	13.3 ± 1.2	268 ± 62	11.2 ± 1.7
Metastasis present	24	13.4 ± 0.6	39.8 ± 3.3	17.1 ± 1.1	5.0 ± 1.3	3.0 ± 2.8	0.91 ± 0.91	13.8 ± 1.4	325 ± 119	10.7 ± 1.2
		$p = 0.206$	$p = 0.002$	$p = 0.688$	$p < 0.001$	$p = 0.036$	$p = 0.049$	$p = 0.055$	$p = 0.030$	$p = 0.101$
Early and late stage group										
Early stage group	105	13.2 ± 0.7	37.0 ± 4.4	17.2 ± 1.2	3.1 ± 0.81	1.8 ± 1.5	0.54 ± 0.48	13.4 ± 1.2	247 ± 47.8	11.5 ± 1.5
Late stage group	635	13.2 ± 0.7	37.4 ± 4.0	16.9 ± 1.2	3.7 ± 1.1	1.8 ± 1.4	0.53 ± 0.49	13.3 ± 1.2	275 ± 67	11.2 ± 1.7
		$p = 0.490$	$p = 0.339$	$p = 0.014$	$p < 0.001$	$p = 0.923$	$p = 0.910$	$p = 0.586$	$p < 0.001$	$p = 0.100$

PT = prothrombin time, APTT = activated partial thromboplastin time, FIB = fibrinogen, FDP = fibrinogen degradation products, DD = d-dimers, RDW = red cell distribution width, PDW = platelet distribution width. Data presented as mean with standard deviation.

Table 2. Predictive value of laboratory indices in the occurrence and staging of nasopharyngeal carcinoma.

Prediction parameter	AUC (95% CI)
The occurrence of nasopharyngeal carcinoma	
PT	0.73 (0.69–0.76)[a]
APTT	0.76 (0.73–0.80)[a]
FIB	0.63 (0.60–0.67)[a]
FDP	0.62 (0.58–0.66)[a]
D-D	0.69 (0.65–0.72)[a]
RDW	0.65 (0.65–0.69)[a]
PLT	0.60 (0.56–0.64)[a]
PDW	0.78 (0.74–0.82)[a]
PT+APTT+PDW	0.88 (0.86–0.91)[a]
T classification (T1-2 vs. T3-4)	
APTT	0.56 (0.52–0.60)[b]
FIB	0.67 (0.63–0.71)[a]
PLT	0.58 (0.54–0.63)[a]
N classification (N0-1 vs. N2-3)	
FIB	0.55 (0.51–0.59)[c]
PLT	0.54 (0.50–0.59)[d]
M classification (Metastasis vs. Non-Metastasis)	
APTT	0.70 (0.61–0.79)[e]
FIB	0.80 (0.70–0.89)[a]
FDP	0.71 (0.62–0.80)[a]
D-D	0.68 (0.57–0.79)[e]
PLT	0.63 (0.48–0.77)[f]
APTT+FIB+FDP	0.84 (0.78–0.91)[a]
Early stage vs. late stage	
TT	0.58 (0.53–0.63)[b]
FIB	0.66 (0.61–0.71)[a]
PLT	0.63 (0.58–0.68)[a]

[a]$p < 0.001$, [b]$p = 0.008$, [c]$p = 0.022$, [d]$p = 0.056$, [e]$p = 0.002$, [f]$p = 0.036$. CI = confidence interval. See Table 1 for other abbreviations.

coagulation components by a direct or indirect route, leading to hypercoagulability and increasing the risk of thrombosis. Thromboembolism is the main cause of death in patients with tumours [4,5]. Although links between abnormal haemostasis and cancer have been described in many malignancies, there are few well-powered clinical studies in nasopharyngeal carcinoma. We contribute to this field with the demonstration of altered haemostasis indices, and red cell distribution width in this disease, and that many indices can predict aspects of the TNM classification.

A prothrombin time prolonged by around 5.5% in our patients suggests a reduction in coagulation factors V, VII and X, and a prolongation of the APTT by 11% in our patients suggests a reduction in coagulation factors VIII, IX, XI and XII), but as other mechanisms may be relevant, the exact reasons for this are unclear. Although the prothrombin time and APTT can predict mortality in patients with a coagulation dysfunction, and more so in advanced disease [7], a prolonged prothrombin time was not linked to prognosis of myeloma patients [8], and in our study, prothrombin time was not linked to clinical staging. We found that APTT is linked to tumour classification (2.2% higher in advanced disease) and metastases (7% higher in metastatic disease), a result consistent with the report that the prognosis of patients with prolonged APTT myeloma is poor [8], and prolonged APTT may be a useful indicator of parenchymal over-involvement in patients with cholangiocarcinoma [9]. Tumour cells are more likely to invade and metastasise due to the decrease of immunity and the

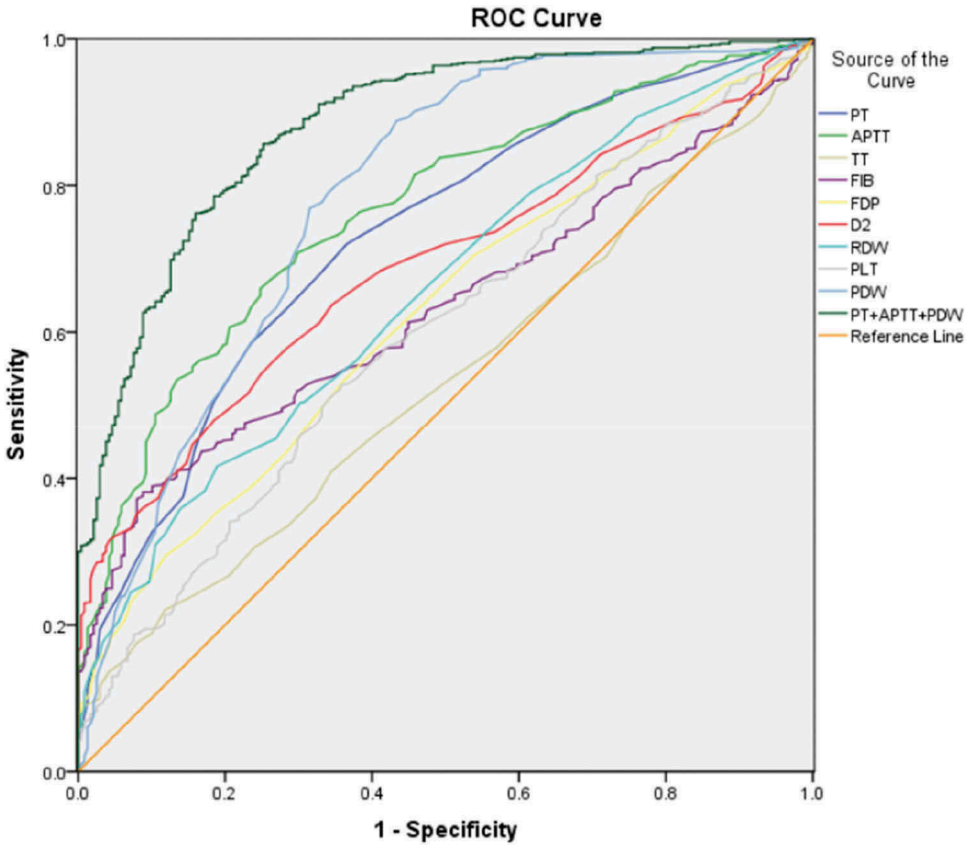

Figure 1. Value of peripheral blood parameters in predicting nasopharyngeal carcinoma.
See Table 1 for abbreviations. All indices significant except thrombin time.

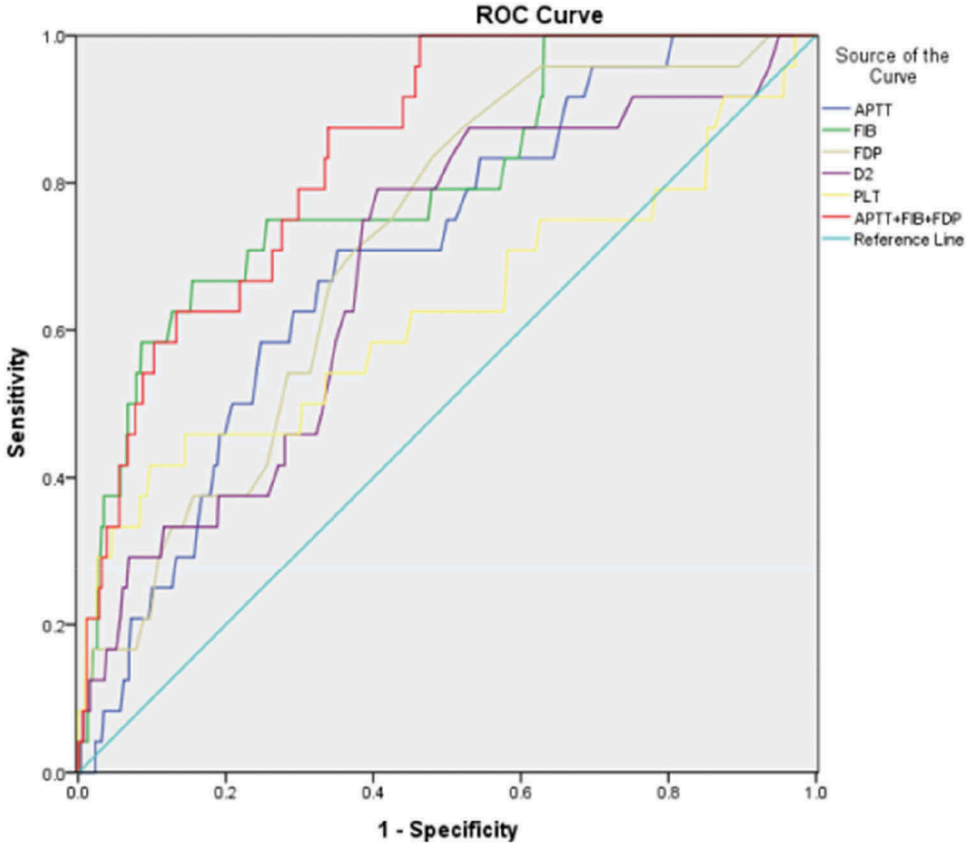

Figure 2. Value of peripheral blood parameters in predicting metastases in nasopharyngeal carcinoma.
See Table 1 for abbreviations. All indices are significant.

decrease of vitamin K synthesis due to liver function injury, which affects the synthesis of coagulation factors and prolongs the prothrombin time and APTT. Thus, use of the APTT may greatly improve the detection rate and clinical aspects of nasopharyngeal carcinoma.

Fibrinogen had good overall predictive value for the diagnosis of all clinical indices: for nasopharyngeal carcinoma it was 16% higher than in controls, for T status it was 15% higher in advanced cases, in N status it was 6% higher, in M status it was 39% higher, and in the late stage of the disease it was 19% higher than in the early stage. These differences may have further clinical implications as fibrinogen is linked to increased blood viscosity, erythrocyte aggregation, and decrease blood fluidity. Our data adds to other literature reporting that fibrinogen is closely connected with clinicopathological features and prognosis, such as gastric, colonic, endometrial, oesophagal and non-metastatic renal cell carcinomas. Prognosis of patients with hyperfibrinogenemia is worse, regardless of pathological stage, and is an independent risk factor for overall survival and recurrence-free survival as well as tumour depth and lymph node metastasis [10–16]. There is ample evidence of the importance of fibrinogen in cancer: it may enhance adhesion between tumour cells and platelets, thus facilitating the formation of emboli, whilst *in vitro* studies showed that fibrinogen plays an important role in the proliferation of tumour cells, the invasion of epithelial-mesenchymal transition, angiogenesis and blood dissemination of tumour cells [17–23].

The final products of fibrinogen degradation are FDPs and d-dimers, and these were, respectively, 31% and 87% higher in nasopharyngeal carcinoma, probably reflecting increased thrombolysis that in turn implies increased thrombogenesis. However, their ability to differentiate clinical indices was absent or weak, suggesting little value in clinical staging. Nevertheless, this does not necessarily contradict reports of potential participation of FDPs in immunomodulation, disease progression and angiogenesis [24,25]. We add to the list of solid tumours with increased d-dimers, such as oesophageal [26], breast [27], lung [28], colon [29] and prostate cancer [30], but we do not find it to be useful in clinical aspects, in contrast to others reporting links with lymph node metastasis in oesophageal cancer and breast cancer [26,27]. Possible reasons include a fundamental difference in the nature of the tumour, and that lymph nodes in the oesophagus and breast are more abundant than in the nasopharynx, so the probability of metastasis is higher.

The red cell and platelet distribution widths were, respectively, 6% higher and 18% lower in nasopharyngeal cancer, but were not linked to any clinical index.

This is in contrast to others reporting that the red cell distribution width can determine prognosis in lung and oesophagal cancer [31,32]. We also report that the platelet count in raised (by 8%) in nasopharyngeal carcinoma, in advanced tumour stage (by 7.7%) and by 11.3% in the late stage of the disease. Increased platelet count had been reported to be associated with poor prognosis in many solid tumours, such as lung, oesophagal, colorectal, and gastric cancer [33–35]. Platelets may participate in the occurrence and development of inflammation by adhering to cells in the vascular wall, triggering autocrine and paracrine activation processes, releasing chemokines, cytokines, proteases and coagulants [36,37], and releasing vascular endothelial growth factor and platelet-derived growth factor, which can stimulate angiogenesis and regulate tumor cell growth [38].

Assessment of a patient based on a single index is poor practice, but combining individual markers can provide a more accurate method for determining clinical features [39]. Accordingly, we selected those indices with good individual predictive value (AUC ≥ 0.7) to determine if a combination of indices provided better data. We found that the combination of prothrombin time, the APTT and the platelet distribution width gave a superior and statistically higher AUC (as determined by non-overlapping 95% confidence intervals) than each index individually for the detection of nasopharyngeal carcinoma. Similarly, the combination of APPT, fibrinogen and FDP gave a superior AUC for the detection of metastases, but the 95% confidence intervals of the combined index overlapped with individual indices, indicating lack of statistical significance. Although combined indices can greatly improve the sensitivity for detecting a particular process or disease, there is often a cost in reduced specificity. Therefore, the value of these two combined markers in judging the occurrence and metastatic status of nasopharyngeal carcinoma needs further study.

We recognise certain limitations to our retrospective study. Although cases and controls were not sex-matched, this is not considered a confounder in coagulopathy. In addition, the differences between the sub-groups studied were often small even though they were statistically significant, and therefore there may be some limitations to use a single measurement to make a clinical decision. Therefore, additional perspective is needed to further analyse the prognostic value of relevant parameters in the diagnosis and management of this disease.

Our data represent an advance in biomedical science because it shows that certain routine haemostasis markers have value in the diagnosis and management of nasopharyngeal carcinoma.

Summary table

What is known about this subject:
- Cancer is a thrombotic disease.
- Little is known of abnormalities in the coagulation pathway in nasopharyngeal cancer.

What this study adds:
- Several individual coagulation indices predict nasopharyngeal carcinoma, but the combination of prothrombin time, APTT and PDW gives the most accurate discrimination.
- Several individual coagulation indices predict metastatic disease, but the combination of APTT, fibrinogen and FDP was the most accurate.

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Disclosure statement

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