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Clinical Significance of CRP/ALB Ratio in Evaluating the Prognosis of Patients with DLBCL

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Abstract

Objective: Exploring the expression characteristics of CRP/ALB (CAR) in DLBCL patients and its value in prognostic judgment. **Methods:** We collected the basic information, clinical characteristics, laboratory examinations and follow-up prognosis of 142 newly diagnosed DLBCL patients with relatively complete data in our hospital and performed statistical analysis. We used X-tile analysis software to obtain the best cut-off value of CAR (0.33), compared the clinical characteristics and survival of patients in the high CAR group and the low CAR group, and compared the survival status with the IPI scoring system. **Results:** 1) There were significant differences in staging, grouping, IPI scores, extranodal involvement, LDH levels, β2-microglobulin, CA125, and Hb levels between the high CAR group and the low CAR group (all $P < 0.05$). 2) According to the survival curve, the OS of the high CAR group was significantly shorter than that of the low CAR group ($P < 0.01$), and the one-year, three-year and five-year survival conditions of high CAR group were all shorter than those of low CAR group. 3) COX analysis showed that high CAR is an independent poor prognostic factor for DLBCL patients. 4) A comparative analysis of OS, three-year and five-year survival showed that the combination of CAR and IPI was significantly better than the IPI system, and there was no significant difference in the evaluation value of the prognosis between CAR alone and IPI alone. **Conclusion:** High CAR value, like the IPI scoring system, is an independent poor prognostic factor of DLBCL, can be used as a reliable indicator of prognosis. And CAR can also be combined with IPI to evaluate the prognosis of DLBCL, of which the effect is better than that of IPI alone.

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Keywords

DLBCL, CRP/ALB, IPI, Prognosis, Significance

1. Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common lymphoma, a type of aggressive lymphoma [1]. According to current domestic and foreign guidelines [2], international prognostic index (IPI) scoring system is still the most commonly used prognostic scoring system for lymphoma such as DLBCL [2] [3] [4] [5]. Researches [6] [7] [8] have shown that many molecular genetic abnormalities, such as the abnormalities of genes BCL-6, BCL-2, P53, MYC and miRNA, are closely related to the poor prognosis of DLBCL. However, these scoring systems are not yet complete and must rely on complete imaging, serological examinations and general assessment of patients, and these examinations are time-consuming, expensive, and limited by technology, so the clinical predictive value has certain limits. Therefore, clinicians need a simpler, faster, and more universal prognostic scoring system.

Recent studies have found [2] [3] [9] [10] [11] [12], tumor-related inflammation and the patient's nutritional status have a certain impact on the prognosis of many malignant tumors, including hematological tumors. Among them, the CRP/ALB ratio composed of inflammation index C-reactive protein (CRP) and nutritional index albumin (ALB) is called CAR (C-reactive protein-to-Albumin Ratio, CAR), which can be used to assess the inflammation and nutritional status of tumor patients at the same time, closely related to the prognosis of tumors [13] [14] [15]. Therefore, this study used a comprehensive clinical analysis of 142 DLBCL patients to explore the characteristics of CAR expression in DLBCL and its relationship with prognosis, in order to evaluate the value of CAR for the prognosis of DLBCL.

2. Materials and Methods

2.1. Case Selection

We selected newly diagnosed DLBCL patients who were hospitalized in our hospital from March 1, 2009 to February 28, 2020, among them, a total of 142 cases had complete follow-up records and relatively complete data. Among the 142 cases, there were 80 males and 62 females, aged from 23 to 85 years (mean age 66.4 years). Each case was confirmed by immunopathological examination, and the diagnosis of DLBCL was confirmed according to the revised fourth edition of WHO classification criterion of lymphoid tissue tumors in 2016. Patients with a variety of acute or chronic infectious diseases, and those with rheumatoid arthritis, systemic lupus erythematosus or other rheumatic diseases and autoimmune diseases that could significantly affect the expression of CRP had been excluded. The patients were divided into two groups according to Hans, including GCB

patients 67 cases (47.2%) and non-GCB patients 75 cases (52.8%).

This study has been discussed, approved and authorized by the Ethics Committee of Taicang Hospital affiliated to Suchow University. And the approval number was KY-2020-180.

2.2. Research Methods

2.2.1. Grouping Method

We collected cases' data of all patients, involving clinical indicators (such as gender, age, clinical stage, symptom grouping, IPI score, number of extranodal involvement, etc.) and laboratory indicators (such as LDH, β2-MG, CA125, Hb, CRP and ALB, etc.). And then we used X-tile software to analyze to get the best cut-off value of the ratio of CRP and ALB (CAR value), which was used as the cutting point (the cut-off value of the two groups) to divide 142 subjects into high CAR group and low CAR group for comparative analysis.

2.2.2. Follow-up Methods

Follow-up was carried out by telephone inquiries, consulting medical records and other methods, and the dead cases were confirmed by consulting the original medical records, and the time of death or the last follow-up time was taken as the termination time of follow-up. The total end time of follow-up was December 31, 2020. The follow-up period was divided into three: 1 year, 3 years and 5 years. The overall survival (OS) was taken as the criterion. OS is defined as the course from the diagnosis of the disease to the death due to this disease or the last follow-up.

2.3. Statistical Analysis

We used X-tile software to get the best cut-off value of CAR, SPSS 23.0 software package for statistical analysis, expressed measurement data as mean ± standard deviation, adopted t-test to compare between the two groups, expressed counting data as percentage (%), adopted chi-square test for data comparison, adopted Pearson correlation analysis for correlation analysis, used COX risk model for multivariate analysis, and employed Kaplan-Meier method to draw survival curve. Furthermore, the receiver operator characteristic (ROC curve) and the areas under the curve (AUV) were compared by MedCalc software. The difference was statistically significant when $P < 0.05$.

3. Results

3.1. The Basic Condition of 142 Patients with DLBCL

In 142 cases, 80 cases were males and 62 cases were females, aged from 23 to 85 years old, with an average age of 66.4 years old. According to clinical stages, 16 cases were in stage I, 47 cases were in stage II, 38 cases were in stage III, and 41 cases were in stage IV. Among them, there were 36 cases in group B (symptomatic group) and 107 cases in group A (asymptomatic group). According to the IPI score, there were 11 cases with 0 points, 37 cases with 1 point, 36 cases with 2

points, 31 cases with 3 points, 17 cases with 4 points, and 10 cases with 5 points. According to the number of extranodal site involvement, there were 87 cases with 1 site involvement, 23 cases with 2, 11 cases with 3, 1 case with 4, 1 case with 5, and 19 cases with no extranodal site involvement.

3.2. Follow-Up Results

All 142 cases were followed up to December 31, 2020. 139 cases (97.9%) completed 1-year follow-up, 108 cases (76.1%) completed 3-year follow-up, and 76 cases (53.5%) completed 5-year follow-up. Until the follow-up deadline, among all the subjects, 99 cases (69.7%) survived and 43 cases (30.3%) died.

3.3. The Relationship between CRP and ALB

CRP is negatively correlated with ALB ($\chi^2 = 26.40$, $P < 0.01$). The specific results are shown in Table 1.

3.4. Comparing in Groups by CAR (CRP/ALB Ratio)

Using X-tile software to get the best cut-off value of CRP/ALB (CAR = 0.33), then we divided 142 patients into high CAR group (CAR > 0.33, 64 cases in total, accounting for 45.1%) and low CAR group (CAR < 0.33, 78 cases in total, accounting for 54.9%).

Patients' high CAR value is correlated with Ann Arbor stages III/IV ($P < 0.001$), group B symptoms ($P < 0.005$), more than 1 site of extranodal focus ($P < 0.05$), IPI scores ≥ 4 ($P < 0.001$), LDH elevation ($P < 0.005$), β2-MG elevation ($P < 0.001$), CA125 elevation ($P < 0.005$) and anemia ($P < 0.001$). In addition, CRP levels increased (100%) in all patients in the high CAR group, while ALB decreased by up to 42.2%. The specific comparison results of clinical and hematological indexes between the two groups were shown in Table 2.

3.5. Survival Analysis

3.5.1. Relationships between CAR, CRP, ALB and Prognosis of Patients with DLBCL

Taking CAR = 0.33 as the cut-off value to analyze its relationship with the prognosis of DLBCL, the result was statistically significant ($P = 0.002$), the median survival time of high CAR group was 15.05 months and that of low CAR group was 23.45 months. The median survival time of high CAR group was obviously shorter than the low CAR group. The specific results are shown in Figure 1. The specific results of 1-year, 3-year and 5-year survival analysis are shown

Table 1. The relationship between CRP and ALB.

Indexes		ALB	
		normal	decrease
CRP	normal	63	9
	increase	33	37

Table 2. The comparison results of each index when CAR's (CRP/ALB) cut-off is 0.33 (statistical analysis by the number of cases).

Indexes	Specific indexes' data	Low CAR group <0.33 (n = 78)	High CAR group >0.33 (n = 64)	χ^2
Gender	Male	41	39	1.00
	Female	37	25	
Age	≤60	19	15	0.02
	>60	59	49	
Stage	I/II	45	18	12.45**
	III/IV	33	46	
Group	A	66	40	9.09**
	B	12	24	
IPI-A	Low-medium low risk (0 - 2)	58	26	16.56**
	Medium high-high risk (≥3)	20	38	
IPI-B	Low-medium risk (0 - 3)	73	42	17.85**
	High risk (≥4)	5	22	
LDH	Normal (109 - 245 U/L)	53	26	10.63**
	Increase (>245.0 U/L)	25	38	
β2-MG▲	Normal (0.80 - 2.20 mg/L)	34	6	19.48**
	Increase (>2.2 mg/L)	20	31	
CA125▲	Normal (0.0 - 35.0 U/ml)	58	29	10.18**
	Increase (>35.0 U/ml)	10	20	
Extranodal focus(es)	1	64	42	5.01*
	≥2	14	22	
Anemia	Yes	21	40	24.42**
	No	57	24	
CRP	Normal (≤10.0 mg/l)	72	0	119.84**
	Increase (>10.0 mg/l)	6	64	
ALB	Normal (35.0 - 54.0 g/L)	69	37	17.45**
	Decrease (<35.0 g/L)	9	27	

Note: 1) *P < 0.05, **P < 0.01, the others are all P > 0.05. 2) ▲: Some cases' data of β2-MG, CA125 at the initial diagnosis were missing, but all the follow-up treatment data were available. Considering the unity of the data, the actual data at the initial diagnosis prevailed in the analysis.

Table 3. The relationship between CAR and prognosis of DLBCL.

Indexes		Overall survival					
		1 year		3 years		5 years	
		<1	≥1	<3	≥3	<5	≥5
CAR	<0.33	20	58	49	29	61	17
	>0.33	27	37	55	9	58	6
	χ^2	4.35*		9.59**		4.06*	

Note: *P < 0.05, **P < 0.01.

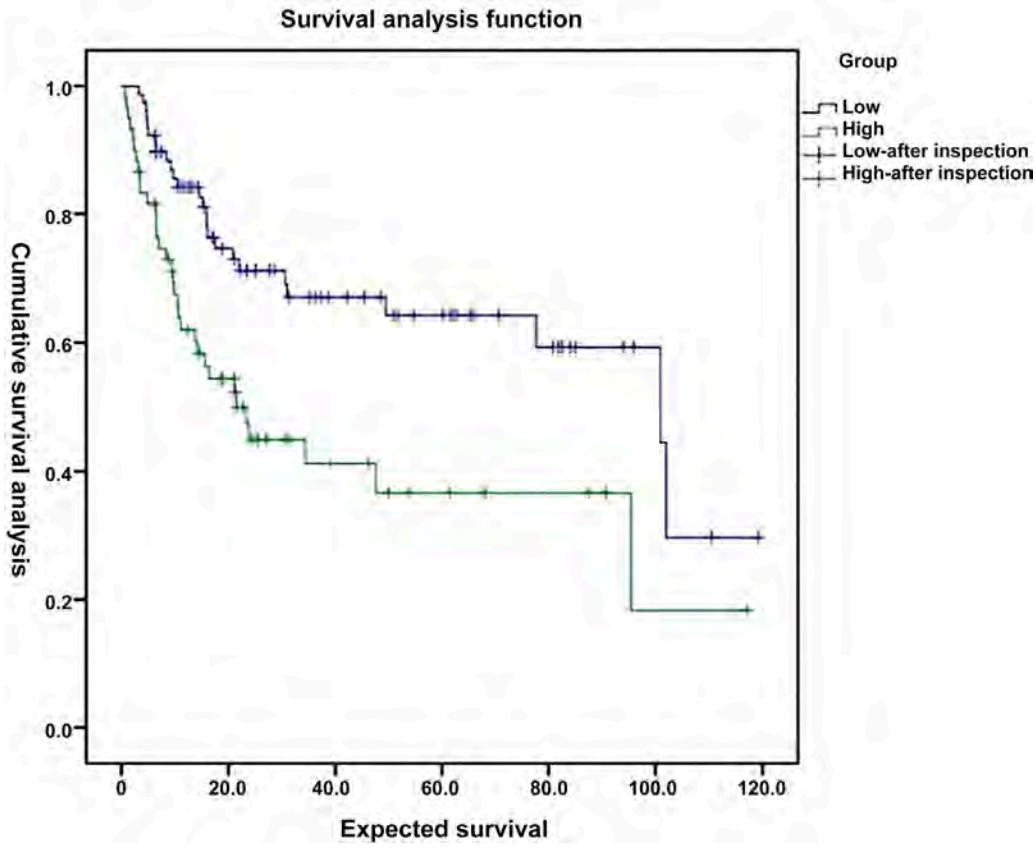

Figure 1. The relationship between CAR and survival and prognosis of DLBCL ($P = 0.002$).

in Table 3. It is shown from Table 3 that high CAR was associated with shorter overall survival of 1-year, 3-year and 5-year in patients with DLBCL.

3.5.2. Analysis of the Relationships between Each Clinical Indexes and Prognosis of Patients with DLBCL

1) Univariate analysis

Univariate analysis was conducted to analyze the relationships between overall survival and 15 indexes such as gender, age, stage and therapies containing Mabthera (R), etc. The results showed that overall survival was related to 6 indexes including the number of extranodal involvement, IPI, LDH, CRP, ALB and CAR. The specific results are shown in Table 4.

2) Multifactor analysis

Multivariate analysis was performed on 4 indicators of extranodal involvement, IPI, LDH, and CAR which were related to overall survival in univariate analysis. The results showed that IPI score (HR: 2.324, 95% CI: 1.304 - 4.142, $P = 0.000$) and CAR (HR: 1.806, 95% CI: 1.049 - 3.109, $P = 0.030$) were both independent prognostic factors of DLBCL (considering that in univariate analysis, CRP and ALB were statistically significant, and the two indexes had been combined into one index of CAR, so there was no separate statistical analysis of these two indexes). Extranodal involvement ($P = 0.62$) and LDH ($P = 0.06$) were no statistically significance.

Table 4. Univariate analysis of the relationships between each clinical indexes and prognosis of patients with DLBCL.

Influencing factors		HR	95% CI	*P*
Gender	male	0.892	0.531 - 1.499	0.67
Age	>60	1.441	0.763 - 2.718	0.26
Stage	III/IV	1.490	0.878 - 2.529	0.14
Group	B	1.501	0.850 - 2.651	0.16
Extranodal involvement	>1	1.881	1.081 - 3.275	0.02*
IPI score	high	2.627	1.541 - 4.476	0.00**
R therapy	no	1.492	0.888 - 2.508	0.13
Anemia	yes	1.572	0.939 - 2.629	0.08
LDH	increase	1.915	1.146 - 3.200	0.01**
β2-MG	increase	1.678	0.883 - 3.186	0.11
CA125	increase	1.389	0.759 - 2.540	0.29
CRP	increase	2.066	1.224 - 3.485	0.01**
ALB	decrease	2.907	1.730 - 4.886	0.00**
D-D	increase	1.858	0.841 - 4.109	0.13
CAR	increase	2.210	1.317 - 3.708	0.00**

Note: *$P < 0.05$, **$P < 0.01$, the other are all $P > 0.05$.

3.5.3. Comparison of Prognostic Significance of CAR Combined with IPI, IPI Alone and CAR on DLBCL

We analyzed the prognosis of CAR combined with IPI and IPI alone, scored 1 point for high CAR and directly superimposed onto IPI score. And we evaluated the prediction accuracy by comparing the area under the receiver operating characteristic (ROC) curve of CAR combined with IPI, IPI alone and CAR. The results showed that no matter the overall survival condition (**Figure 2(a)**) or the three-year and five-year survival condition (**Figure 2(c)** and **Figure 2(d)**), the significance of IPI combined with CAR to prognosis was higher than IPI alone, that is, CAR combined with IPI had better prognostic value than IPI alone, while it had little effect on 1-year survival time (**Figure 2(b)**). Comparing the ROC curve of IPI with CAR, the area under the curve of CAR was larger than all that of IPI in 1 year, 3 years and 5 years, but the difference was not statistically significant.

4. Discussion

At present, the discussion on the relationship between inflammation and tumor has become a hot research topic [10] [16] [17]. On the one hand, tumor-related inflammation can mediate and inhibit tumor progression [18], on the other hand, it can also play a counterproductive role, stimulating tumor cell growth, proliferation and tumor angiogenesis, accelerating tumor invasion and metastasis [19] [20] [21]. As an accurate and reliable indicator of inflammation, CRP is

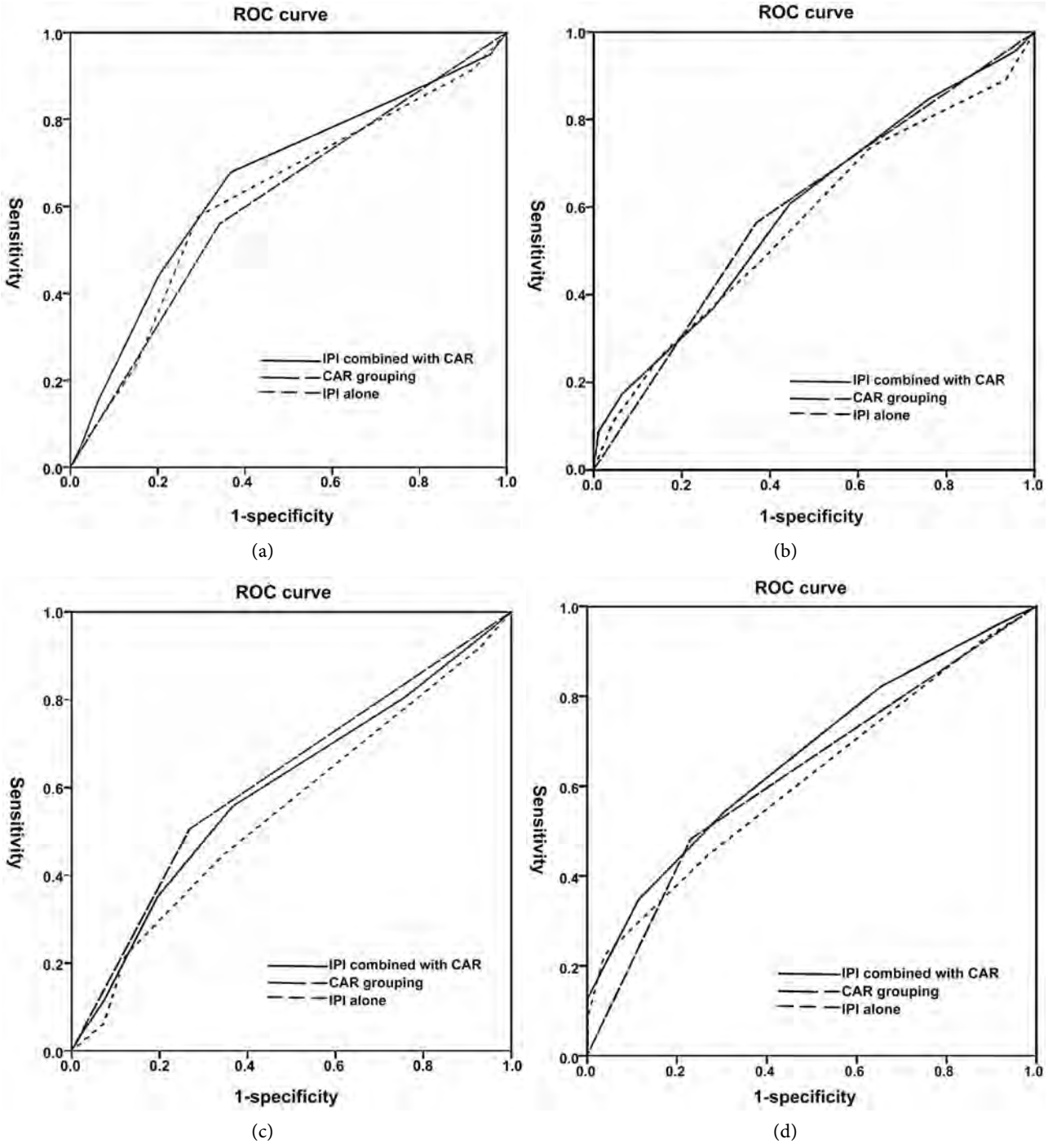

Figure 2. (a) ROC curve comparison of the prognostic value of CAR alone in overall survival condition (IPI combined with CAR versus IPI alone, $P = 0.02$; IPI versus CAR, $P = 0.86$); (b) ROC curve comparison of the prognostic value of CAR combined with IPI and IPI alone in 1-year survival condition (IPI combined with CAR versus IPI alone, $P = 0.11$; IPI versus CAR, $P = 0.68$); (c) ROC curve comparison of the prognostic value of CAR combined with IPI and IPI alone in 3-year survival condition (IPI combined with CAR versus IPI alone, $P = 0.01$ and IPI versus CAR, $P = 0.32$); (d) ROC curve comparison of the prognostic value of CAR combined with IPI and IPI alone in 5-year survival condition (IPI combined with CAR versus IPI alone, $P = 0.02$; IPI versus CAR, $P = 0.91$).

produced by hepatocytes and epithelial cells under the stimulation of IL-6, IL-1, TNF and other inflammatory factors, which is not only related to the poor prog-

nosis of tumors, but also increases the occurrence risk of future tumors [22] [23]. Researches [24] [25] [26] [27] have found that the association between increased circulating levels of CRP and increased cancer risk is not directly causal. In order to better predict the prognosis of tumors, the researchers proposed to combine CRP with ALB, which is an indicator of nutritional status, into a new indicator, CRP/ALB (CAR), to predict the prognosis of cancer patients [12] [13] [14] [28]. Domestic and foreign researches [12] [13] [14] [28] [29] [30] have proved that, in solid tumors such as pancreatic cancer, gastrointestinal tumors, lung cancer and reproductive system, CAR can independently predict the prognosis of patients.

This study took CAR = 0.33 as the best critical value, which is basically consistent with the current domestic and foreign researches' CAR value of 0.03 - 0.68 [14] [15] [31]. We selected the data of patients at the time of initial diagnosis, which were more representative, stable and uniform, and can better judge the predictive value of CAR value at the time of initial diagnosis. In this study, the differences in staging, grouping, number of extranodal involvement sites, IPI score, LDH level, β2 microglobulin, CA125, and anemia between the high CAR group and the low CAR group were statistically significant, which indicated that patients in the high CAR group had more serological abnormalities and more serious clinical symptoms risk [30]. Moreover, the OS of the high CAR group was significantly shorter than that of the low CAR group, and the median survival time was 8.4 months less in the lower CAR group. This suggested that high CAR level was closely related to the poor prognosis of DLBCL, of which the result was consistent with the results of solid tumors [29] [30] [32].

The single-factor and multi-factor COX survival analysis of CAR in DLBCL showed that both CAR and IPI scores were independent prognostic factors for DLBCL (CAR: HR = 1.806, $P = 0.03$; IPI score: HR = 2.234, $P = 0.00$). To further evaluate the prognostic value of CAR, this study also combined CAR and IPI scoring system to form a new scoring system to evaluate the prognosis of DLBCL. ROC curve results showed that CAR and IPI have no significant difference in the assessment of survival (the overall survival time, 1-year, 3-year and 5-year survival, P all > 0.05). When assessing the overall survival and three-year and five-year survival of patients, CAR combined with IPI had a better predictive value for the prognosis of DLBCL patients than the IPI scoring system alone ($P = 0.02$, 0.01 and 0.02, respectively).

Therefore, the CAR value, like the IPI scoring system, is an independent poor prognostic factor of DLBCL, which can be used as a reliable indicator to judge the prognosis, and it is easy to obtain. CAR combined with IPI scoring system has better prognostic value than IPI scoring system alone. However, this study is a single-center preliminary study, the number of DLBCL cases included is not too large, and the time span for selecting cases is also long, there may exist information bias, loss to follow-up, etc. Therefore, it needs to further expand the number of cases, extend follow-up time, conduct multi-center, prospective and other unified standards to further study.

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All authors read and approved the final manuscript.

Conflicts of Interest

No potential conflict of interest was reported by the author(s).

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Large Vessel Vasculitis in a Patient with Systemic Lupus Erythematosus Presenting as Takayasu's Pulseless Arteritis

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Abstract

Systemic lupus erythematosus (SLE) with an associated aortoarteritis presenting as an ischemic stroke is a rarity in the medical literature. We report the case of an 11-year-old male presenting with an acute ischemic stroke meeting the criteria for the diagnosis of SLE and findings consistent with an aortitis on imaging but mimicking the diagnosis of Takayasu's pulseless arteritis. Blood and imaging investigations revealed the finding of SLE aortitis following an acute stroke presentation. Thus, it is imperative to note that even though it is infrequent, SLE can be associated with a large vessel vasculitis.

Keywords

Systemic Lupus Erythematosus, Aortoarteritis, Takayasu's Pulseless Arteritis

1. Introduction

It is well recognized that the two common causes of large vessel arteritis are giant cell arteritis and Takayasu's pulseless arteritis [1]. A less well known, cause is SLE especially SLE affecting the aorta and the great vessels arising from the aorta [2]. It is not uncommon for an ischaemic stroke to be caused by SLE but the pathophysiology usually involves vasculitis affecting smaller vessels and or increased stickiness of the blood itself [3].

There is a myriad of etiologies for stroke presentation in the younger population. Strokes in the pediatric groups of patients are relatively rare in which the reported incidence of strokes (ischemic and hemorrhagic) in children under 18 years old was reported to be 1.2 to 13 cases per 100,000 patients [4].

Etiologies of strokes range from cardio embolic phenomena, atherosclerosis

and inflammatory diseases [5]. Vasculitis can lead to aneurysm formation or stenoses of the affected blood vessels which can result in limitation of blood flow to the brain resulting in stroke [6].

In this case report, the patient presented with an acute ischemic stroke in which the etiology was revealed as a lupus arteritis presentation with an associated large vessel vasculitis (aortitis); a rare occurrence as noted throughout the medical literature.

2. Case Report

This is the clinical case report of an 11 year old Afro-Caribbean boy who presented with sudden onset of left upper limb and left lower limb weakness over a period of 2 days. The patient had a background history of a normocytic anaemia which was previously being investigated. Prior to this, there was one hospital admission 2 years ago when the patient presented with arthralgia and chest pain for which no definitive diagnosis was made at the time.

There were also complaints of facial twisting, slurred speech, intermittent diplopia and generalized headaches associated with two isolated episodes of fever.

On physical examination on admission, the boy was noted to have a BP 114/66 mmHg, a tachycardia of 117 beats per minute and he was tachypneic with a temperature of 37.9 degrees Celsius. His oxygen saturation on room air was 97% and his random blood glucose was recorded as 113 mg/dL. There was a grade 2/6 ejection systolic murmur noted in the aortic region with no radiation. Auscultation of the chest and abdominal examination were both unremarkable.

On neurological examination, his Glasgow coma scale score was 15/15 and the patient was oriented to time, person and place. Visual field testing revealed a left incongruous homonymous hemianopia. Fundoscopy was normal. A left upper motor facial weakness was present. Bulbar function and speech were normal.

On limb examination, tone was markedly reduced in the left upper and lower limbs. The power of the left upper and lower limb was 0/5, whilst the power of the right upper and lower limb was 5/5. The patient was hyperreflexic throughout with left ankle clonus and a left up going plantar response. There were no abnormal cerebellar or sensory findings and the gait could not be assessed.

Both radial and the right posterior tibial pulses were palpably absent.

3. Results

CT brain without contrast revealed wedge shaped hypo densities in the right superior fronto-parietal region as shown below in **Figure 1**.

On contrast administration, there was no enhancement of the lesions.

MRI/Angiogram brain demonstrated a large right cerebral infarct involving the right middle cerebral artery territory mainly, plus an absent right internal carotid artery and attenuation of the right middle cerebral artery (**Figure 2** and **Figure 3**).

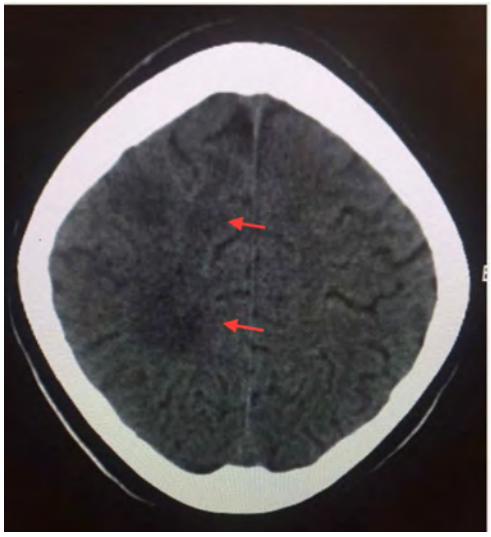

Figure 1. CT brain non contrast demonstrating hypo densities in right superior fron-to-parietal region.

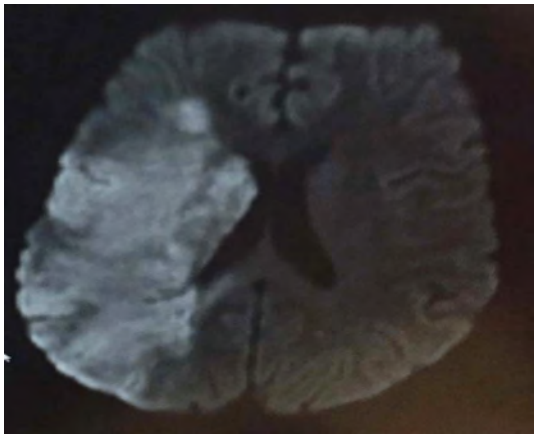

Figure 2. MRI Brain Scan showing large right cerebral infarct.

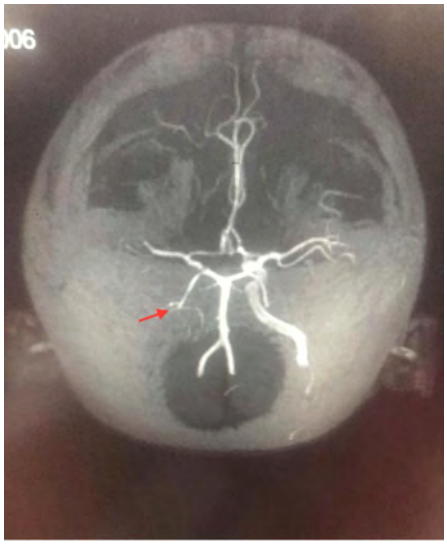

Figure 3. absent right internal carotid and attenuation of the right middle cerebral artery.

CT angiogram showed a filling defect in the proximal right common carotid and abnormalities in the aortic arch consistent with inflammatory disease (Figure 4 and Figure 5).

A normocytic normochromic anaemia was noted with a Hb 8.6 g/dL. There was no renal impairment with a Cr 1.0 and electrolytes all within normal limits. Liver function tests were within normal limits while the erythrocyte sedimentation rate (ESR) was >125 $mmhr^{-1}$ and C-reactive protein was elevated 242 mg/dL.

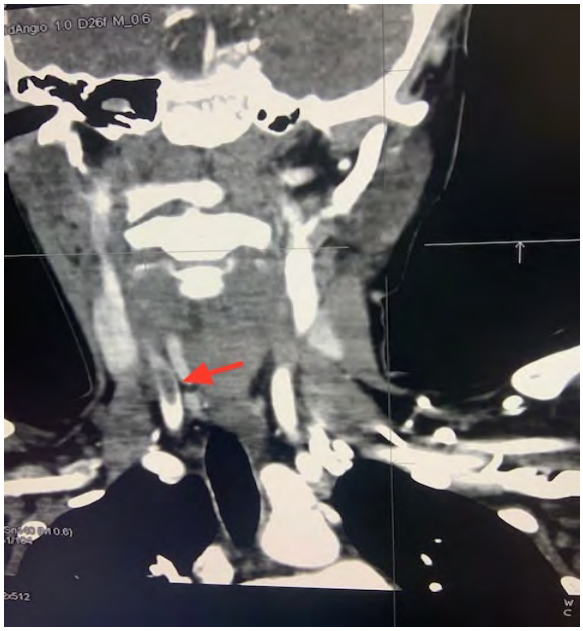

Figure 4. CT carotids showing a central filling defect in the proximal aspect of the right common carotid artery.

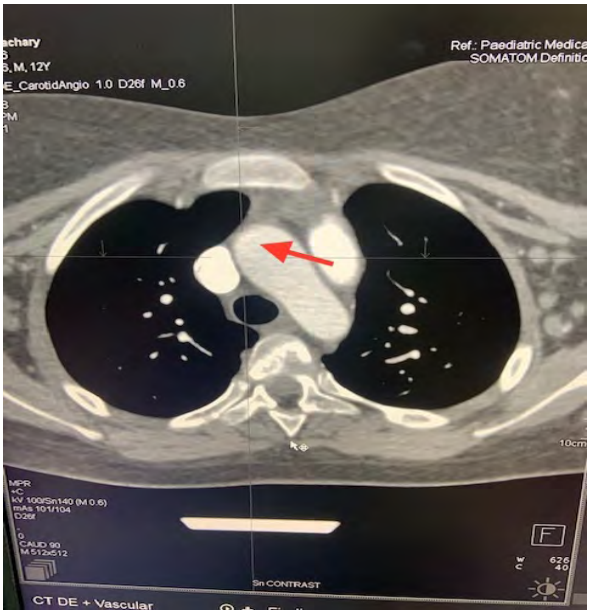

Figure 5. CT chest angiogram demonstrating hypo densities seen in intimal wall of the aortic arch.

Fasting lipid profiles were as follows Total Cholesterol 146 mg/dL, TG 119 mg/dL, HDL 21 mg/dL, LDL 102 mg/dL and VLDL 24 mg/dL. Coagulation studies and thyroid function were within normal limits. Other significant investigations were as follows as shown in Table 1.

ECG showed normal sinus rhythm and transthoracic echocardiogram done on 2 separate occasions demonstrated a normal left ventricle and valves without any evidence of thrombus, vegetation or shunts.

4. Management

Before the results of the autoimmune screen (ANA, dsDNA) were available, the initial thought was a diagnosis of Takayasu's pulseless arteritis.

The patient was treated with methylprednisolone 1 g iv od for 3 days followed by high dose prednisolone on alternating days. He became drowsy whilst his ESR remained > 125 $mmHr^{-1}$ following steroid administration.

Table 1. Blood investigations.

HIV Rapid Test	Negative
Hb Electrophoresis	A1 + A2
Sickle Cell Test	Negative
Urine Cocaine	Negative
Urine Marijuana	Negative
VDRL	Non reactive
Hb A1c	4.6%
HepBsAg	Negative
Anti-HCV	Negative
Rheumatoid Factor	Negative
Blood culture × 4	NBG
Urine Culture	NBG
Urinalysis	NAD
ANA	Positive
Anti-dsDNA	67.19 (Positive)
ANF	126.85 (Positive)
Homocysteine	6.3 (normal)
pANCA	32.76 (elevated)
cANCA	63.83 (elevated)
Anti-thrombin	Not done
Protein C	122 (normal)
Protein S	6.9 (low)
Factor V leiden	2.21 (normal)
Anti-cardiolipin antibodies	negative

Prednisolone was then switched to dexamethasone 4 mg iv tid. However, the boy looked distinctly unwell and his ESR still remained persistently elevated above 125 $mmHr^{-1}$.

There was a new complaint of visual blurring of the right eye. Fundoscopic examination revealed a pale retina and possibly early optic atrophy of the right eye (**Figure 6**).

Intravenous immunoglobulin (IVIG) (0.4 g/kg/day) was then administered for 5 days.

After a small number of days there was slow but steady improvement in the patient's overall condition. Daily physiotherapy and stroke rehabilitation were instituted after which the patient was discharged on oral prednisolone and followed in the outpatient clinic.

Two weeks later the boy appeared better. His peripheral pulses returned and the ESR started to trend downward. One month later, he was walking with help but left arm function was still very much impaired. He remains on a reducing dose of oral prednisolone.

5. Discussion

There is a paucity in the literature of reported cases demonstrating patients diagnosed with SLE having an associated large vessel vasculitis. The classic large vessel vasculitides include giant cell arteritis and Takayasu's arteritis [1]. In one case report, there was an associated large vessel vasculopathy in a Japanese patient with a background diagnosis of SLE and temporal arteritis [7]. We found a similar case to ours where there was a patient with a Takayasu's arteritis presentation followed by an associated diagnosis of SLE [8]. In this reported case, the patient was a 24 year old Indian female who initially presented with clinical symptoms and signs consistent with a diagnosis of Takayasu's pulseless arteritis. Three years later she then represented with rash, arthralgia, non scarring alopecia and other clinical features of SLE [8]. In our case, the patient similarly presented originally with clinical features more consistent with a diagnosis of Takayasu's pulseless arteritis but with a much more persistently elevated ESR. In

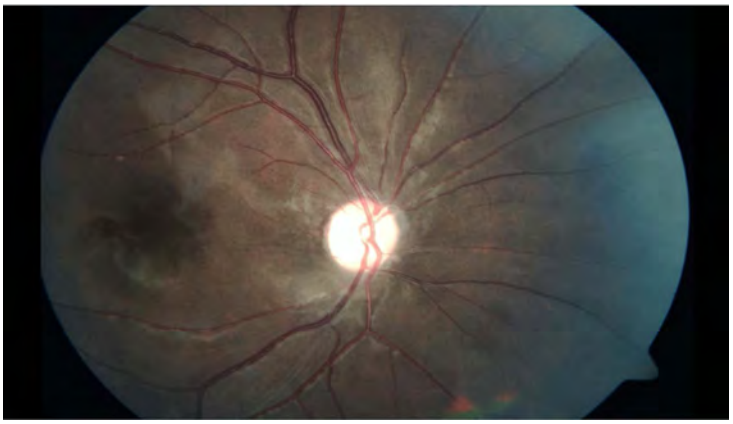

Figure 6. Retinal image demonstrating pale retinal background.

our patient, the diagnosis of SLE was made on the same admission and based on the previous complaints of arthralgia plus the positive autoimmune blood investigations.

Of note, there have been reported cases of non specific aortitis involving the aorta and its main branches with non specific symptomatology unfulfilling the diagnostic criteria for SLE [9]. Aortoarteritis is more prevalent in Japan and Afro-asian countries and has been noted to rarely be associated with SLE [10].

Another differential diagnosis worthy of mention includes a study by Wichremasinghe *et al.* [11]. They reported a small number of patients with emboligenic aortoarteritis where thrombi formation occurred from a transient form of focal aortoarteritis involving the medial elastic tissue of the aorta. This led to a potential etiology for an ischemic stroke in the younger population. None of their patients had a diagnosis of SLE. It is plausible that our patient could have had thromboembolism from inflammatory disease of the aorta and one of its main branches giving rise to the middle cerebral occlusion and possibly the right ophthalmic artery as well.

The boy presented with what appeared to be a good fit for the diagnosis of Takayasu's pulseless arteritis. The absent pulses, involvement of the aorta and great vessels and raised ESR were well in keeping with this diagnosis [12]. However, Takayasu's pulseless arteritis is seen primarily in Asian women and is not associated with lupus antibodies [8] [13]. Furthermore, there have not been any reported cases of Takayasu's pulseless arteritis in the Caribbean population plus SLE is a relatively common disorder in people of Afro-Caribbean descent [14] [15]. Our patient met the criteria for the diagnosis of SLE based on the EULAR/ACR scoring scale [16].

6. Conclusion

Even though the occurrence of SLE associated with a large vessel vasculitis is an unusual occurrence in the medical literature, the incidence is important to note as it can impact on the outcome of patients' morbidity and mortality.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

SLE: Systemic lupus erythematosus

ESR: Erythrocyte sedimentation rate

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Faster Healing Process by Sparing Intramural Myoma's Pseudocapsule during Laparoscopic Myomectomy Compared with Removing It during Open Myomectomy

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Abstract

Uterine fibroids are the most common benign tumours in the reproductive system. They are proliferations of smooth muscle cells of the myometrium containing a large quantity of extracellular matrix and they are surrounded by a pseudo capsule of compressed areolar tissue and smooth muscle cells. They can cause various symptoms such as menorrhage, pain and infertility and therefore they can be a traumatic experience for several women. The treatment of choice is myomectomy. In the past, myomectomy was performed by relatively atraumatic techniques, which involved stretching the myoma from its pseudocapsule to extract the fibroid directly from the surrounding fibromuscular tissue, breaking up the fibrous bridge. Modern laparoscopic intracapsular myomectomy (LIM), however, leaves the fibrovascular network surrounding the myoma (namely the "fibroid neurovascular bundle") intact which reduces the bleeding and/or uterine musculature trauma, and spares the neuropeptide fibers of the pseudocapsule. In this observational study, we com-

pare the two techniques-laparoscopic intracapsular myomectomy (LIM) and conventional abdominal myomectomy (CAM) regarding the longterm uterine healing and a significantly faster healing process of the uterine incision was achieved by LIM compared to CAM.

Keywords

Myomectomy, Laparoscopic Intracapsular Myomectomy, Healing

1. Introduction

Uterine leiomyomas, (also known as fibroids or myomas), are the most common benign tumours in the reproductive system of childbearing age women, with a prevalence of 30% - 35% [1] [2] [3]. However, fibroids typically regress during menopause since they are oestrogen dependent.

Uterine leiomyomas are proliferations of smooth muscle cells of the myometrium containing a large quantity of extracellular matrix (fibronectin, collagen, proteoglycan), and are surrounded by a pseudocapsule of compressed areolar tissue and smooth muscle cells. This pseudocapsule contains very few blood vessels and lymphatic vessels.

Myomectomy is the treatment of choice for symptomatic women who have symptoms and who wish to preserve their future fertility. The overall risk of uterine rupture during pregnancy or labour after myomectomy is 2.4/1000 between 29 and 35.5 weeks and is attributed to the extensive muscular damage or excessive use of diathermocoagulation [3]. To minimize the risk, preservation of the uterine anatomical and functional integrity during myomectomy, especially in women of reproductive age, is of imminent importance. The restoration and maintenance of the physiologic function of the uterus is or should be, the ultimate goal of surgical treatment.

In the past, myomectomy was performed by relatively atraumatic techniques, which involved stretching the myoma from its pseudocapsule to extract the fibroid directly from the surrounding fibromuscular tissue, breaking up the fibrous bridge. Modern laparoscopic intracapsular myomectomy (LIM), however, leaves the fibrovascular network surrounding the myoma (namely the "fibroid neurovascular bundle") intact which reduces the bleeding and/or uterine musculature trauma, and spares the neuropeptide fibers of the pseudocapsule. This more recent approach has a favourable impact on the uterine healing and successive functionality, has simplified the surgical procedure and minimised the concerns over blood loss, post-surgical adhesion and wound healing [4] [5]. Using the LIM techniques, the risk of uterine rupture during future pregnancy or labour, appears to be decreased, although the issue is still under debate.

The quality of healing of the myometrial incision after myomectomy can be evaluated by ultrasound [6] [7].

The objective of the present prospective observational study was to compare conventional abdominal myomectomy with LIM in premenopausal women in order to assess the quality of uterine healing.

2. Materials and Methods

A prospective observational study was performed from January 2017 to December 2020 in order to compare laparoscopy intracapsular myomectomy (LIM) with conventional abdominal myomectomy (CAM) with removal of the pseudocapsule in premenopausal women. LIM was performed at IAKENTRO IVF Center and CAM was performed at the University Hospital of Ioannina.

This study was approved by the local Ethics Committee of both institutions. Informed consent was obtained from all participants prior to their inclusion in the study.

2.1. Inclusion and Exclusion Criteria

Study participants were women of reproductive age with an indication of myomectomy who required preservation of their future fertility. All of the participants were of caucasian origin. The myomas were intramural or sub-serous (FIGO types 3 - 6) of 4 - 14 cm diameter. The exclusion criteria included: no other gynaecological diseases detected on preoperative ultrasound, no previous history of pelvic or abdominal surgery or pelvic inflammation, suspicion of genital cancer and/or uncertain pathology of genital tract, presence of, adnexal masses, endometrial hyperplasia with or without atypia. Suspected adenomyosis and/or adenomyosis were also excluded from the study (Table 1). The patients' demographics, such as mean age (standard deviation [SD]), parity, body mass index (BMI; kg/m^2), were recorded (Table 2).

2.2. Study Protocol

Preoperatively all patients were evaluated preoperatively by transvaginal ultrasound within 30 days before surgery in which the number of myomas, size and location were recorded. A pelvic magnetic resonance imaging (MRI) with contrast

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion criteria
1) Reproductive age	**1)** No other gynaecological diseases detected on preoperative ultrasound
2) Caucasian Origin	**2)** No previous history of pelvic or abdominal surgery or pelvic inflammation or suspicion of genital cancer
3) Fibroids (intramural or sub-serosal confirmed with investigation (pelvic scan, MRI, CT)	**3)** No uncertain pathology of genital tract, such as presence of adnexal masses, endometrial hyperplasia with or without atypia.
4) No suspected adenomyosis	

Table 2. Epidemiologic characteristics of patients included in the study. LIM: laparoscopy intracapsular myomectomy; CAM: conventional abdominal myomectomy.

Characteristics	Overall (n = 106)	LIM (n = 75)	CAM (n = 31)
Age (years)	32.5	34	31
BMI (kg/m^2)	27	25	29
Nulliparous	88	62	26
Infertility	93	65	28
Number of Fibroids	2.6	2.2	3.1
Previous Abdominal surgery	31	23	8
Diameter of fibroids (mm)	77.5	75	80

medium also was also performed the same period in order to confirm the findings of the transvaginal ultrasound and detect a potential leiomyosarcoma. At the end of the surgery the extracted myomas were sent for histological evaluation.

Myomectomies were performed between day 7 and day 17 of the menstrual cycle. During this interval, oestrogen proliferative activity has not yet maximized endometrial thickness, while uterine vascularization is more limited compared to the second luteal phase of menstrual cycle. No preoperative treatment with GnRH analogues or Ulipristal Acetate was used in either group.

In order to evaluate and compare the healing process, all patients were monitored postoperatively by ultrasound on days 7, 30 and 90 after the operation (**Table 3**). All women were advised to avoid any pregnancy for the first three months postoperatively and were all asked subsequently to set report potential adverse outcomes or conception.

The surgical protocol and LIM technique have been described in detail in previous studies [6]. Evaluation of wound healing assessed progressive decrease of uterine incision size (initial, final and % difference), time period of healing and the existence of anechoic areas, hematomata.

As wounds fail to progress through normal stage of healing, they become more differential regarding shape, size and the extent of tissue damage, which is compounded by the absence of uniformly acceptable wound healing diagnostic methods.

3. Statistics

Continuous variables were expressed as mean ± SD, while categorical variables as n (%). Kolmogorov-Smirnov test was used to assess normality of values distribution for continuous variables. Chi-square test was used to compare categorical variables, while continuous variables were compared with Independent samples t-test in case of normally distributed values or Mann-Whitney test in case of abnormally distributed values. Statistical analysis was performed with Statistical Package for Social Science 21.0.

Table 3. Final outcomes comparing the two techniques.

Surgical Outcomes	LIM (n = 75)	CAM (n = 31)
Primary Outcomes		
Uterine incision (maximum, cm)	2 ± 0.6	3 ± 0.8
Time period to healing (days, mean ± SD)	28 ± 8.2	37 ± 9
Operative time (min; mean & SD)	65.4 ± 24.3	87 ± 34
Urologic injury	0	0
Intestinal Injury	0	1
Vascular Injury	0	0
Decrease of postoperative Hb (gr/dl)	1.6 ± 0.8	2.8 ± 0.5

4. Results

Overall, 106 women were included in the study, out of which 75 in the LIM group (group 1I) and 31 in the CAM group (group II).

Mean number of extracted myomas was 2.2 for group I and 3.1, for group II, while mean diameter of the largest myoma was 75 mm in group I and 80 mm in group II. Epidemiological characteristics of patients are presented in **Table 1**.

On the 7th postoperative day, the site of the LM or AM scar appeared as a highly echogenic area with profuse blood flow at the periphery in all cases. Four patients (4%) had a hematoma, in group II, which appeared as a hypoechoic area with areas of echogenicity. The anechoic-hypoechoic area was almost avascular (volume 15 cm^3, 21 cm^3, 91 cm^3 and 95 cm^3).

By the 9th postoperative month, the LM or AM healing area had regained the echogenicity of normal myometrium, however a hematoma appearing as a hypoechoic area, with decreased volume from 95 cm^3 to 9 cm^3 and from 91 cm^3 to 5 cm^3 3 was still present in 2 cases. The non-operated myometrial areas showed significantly more prominent blood flow than the healing areas.

The time period until healing was significantly increased in CAM ($P = 0.001$). Wound sign disappeared in 90% of the patients 30 days postoperatively in group I but in only 30% in group II. However, ultrasonographic wound signs disappeared in all study patients on the 90th postoperative day. Estimated blood loss and, operative time were significantly lower in cases treated with LIM. This is obvious as the dissection of myoma is easier leaving the pseudocapsule and the bed of the myomectomy is usually free from haemorrhage.

5. Discussion

This prospective observational study showed a significantly faster healing process of the uterine incision with LIM to sparing the psedocapsule compared to CAM.

This finding reflects the clinical observation that sparing the pseudocapsule reduces surgical trauma, leaves less myometrial defects, uses less or no electrocautery and therefore enables a faster healing process.

Generally, an optimal myomectomy aims to preserve the integrity of the extra-

cellular matrix, either performed via laparoscopy or laparotomy, as this ensures the three-dimensional organization of the myometrium after myomectomy [8] [9]. This is especially important in women of reproductive age who have not yet completed their family.

In recent years, laparoscopic myomectomy has been considered as an alternative of laparotomy with numerous advantages including shorter hospitalisation, less need for analgesia, lower intraoperative blood loss and a favourable outcome in a subsequent pregnancy. Although uterine rupture during pregnancy, labour or delivery may still occur, the risk is low.

The wound healing process begins with the inflammatory phase lasting up to 72 h during which pain, swelling, redness and increased local temperature are common symptoms. Accumulation of exudates and edema begins the process of tissue repair following injury when a blood clot forms and seals the area. In muscular injuries, a myofilament reaction takes place and peripheral muscle fiber contraction occurs within the first 2 h. Edema and anoxia results in cell damage and death within the first 24 h, and the release of protein breakdown products from damaged cells leads to further edema, tissue hypoxia and cell death. Phagocytosis then begins to rid the area of cell debris and edema [10]. The muscular regeneration and repair occur during the fibro-elastic/collagen-forming phase, which lasts from 48 h up to 6 weeks. During this time, structures are rebuilt, and regeneration occurs. Fibroblast cells begin to produce Type III collagen at 4 days, and fiber organization is random and immature. Capillary budding occurs, bringing nutrients to the region, and collagen cross-linking begins. As the process proceeds, the number of fibroblasts decreases as more collagen is laid down. This phase ends with the beginning of wound contracture and shortening of the margins in the injured area. The last phase of healing is the remodeling phase, which lasts from 3 weeks to 12 months. Gradually, cross-linking and shortening of the collagen fibers promote the formation of a tight, strong scar. Final aggregation, orientation and arrangement of collagen fibers occur during this phase. Healing of the injured muscle does not fully restore muscle to its prior state, as fibrous scar tissue slows muscle healing. The two processes of healing and fibrosis compete and impair complete regeneration [11]. Many of these processes are catalysed by growth factors such as transforming growth factor-beta 1 (TGF-b1), a ubiquitous substance that initiates a cascade of events that activate both myogenesis and fibrosis, and decorin, a proteoglycan that impedes fibrosis by binding to TGF-b1 [12]. These growth factors are under active investigation to determine their role in muscle healing.

Myomectomy always causes trauma due to the visceral peritoneal incision, opening of the myometrium, removal of the fibroid and closure of the muscle margins by suture. Each major structural and vascular disruption during myomectomy leads to a classical inflammatory reaction and causes irreversible tissue damage and cell necrosis with two plausible options. A regenerative response results in an optimal reconstruction of the damaged tissue and a high-quality

muscle scar. A fibrotic response results in a poor reconstruction of the myometrium and a fibrotic and inelastic scar. In the first case, the myometrium returns to full function, while in the second case the result is tissue dysfunction characterised by pain, inflammation and altered internal tissue stress. The injury may result in progressive functional disability and a higher risk of uterine rupture during pregnancy or during labour. The progressive evolution of the uterine scar from a highly echogenic area with an ill-defined heterogeneous myometrial texture to a normal echoic area confirms a normal healing process, whereas a fibrotic scar continues to display hyper or hypoechogenic areas and increased mean scar diameter.

When surgeon gently removes the UF through the pseudocapsule with selective coagulation of its vessel, they preserve the muscle surrounding UF and avoids excessive bleeding, returning it to normal healthy uterine tissue. Extensive diathermocoagulation and excessive i.m. bleeding generally worsens the healing process and myometrial function in subsequent pregnancy [12].

Moreover, some of the pseudocapsule vessels join at the base of the UF creating a little foot that often bleeds during an extra-capsular myomectomy, which creates a hematoma, manifestating as avascular echoic area.

The myometrial area of the scar after myomectomy can be evaluated by 2D ultrasound and Doppler velocimetry, a non-invasive and, safe method that assesses uterine perfusion, the presence of post-operative hematoma and disechogenic, heterogeneous, or an ill-defined scar area, all unfavourable signs for myometrial scarring.

6. Conclusions

Intracapsular myomectomy enhances myometrium integrity peripheral to the fibroid site, by preserving the neurovascular bundle and neurotransmitters surrounding fibroids, for uterine healing and myometrium restoration after surgery. Moreover, allowing correct myometrial healing, intracapsular myomectomy could preserve reproductive outcomes and normal labour and delivery and permit less bleeding, better neurovascular bundle sparing for scar quality and reductions in post-operative adhesions. Increasing knowledge of the pseudocapsule angiogenesis and neurovascular fibers could play an important role in understanding the origin and recurrence of uterine leiomyomas, therefore allowing for optimal treatments.

In the present study, we demonstrated that dissection of the fibroid should run inside the avascular plane, leaving the pseudocapsule around the outside. The bed of the myomectomy is usually free from haemorrhage at the end of dissection if care has been taken to follow the avascular cleavage plane; there is no need to take further steps for haemostasis. Therefore, independent of the way of surgery laparoscopy or abdominal this study has demonstrated that there is no need to. Remove the pseudocapsule during myomectomy, which is independent of the use of a laparoscopic or abdominal surgical procedure.

In conclusion, the current study has shown that a faster healing process is expected after laparoscopic myomectomy when the intamural myoma's pseudocapsule is spared compared with its removal during open myomectomy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Update on Carotid Stenting and Endarterectomy

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Abstract

The role of carotid stenting and endarterectomy has been evolving over the past few decades. Results of recent randomized trials have added more insights to the indications of the two established interventions for symptomatic moderate to severe stenosis as well as asymptomatic carotid stenosis. Despite a wide range of complication rates in various trials for both symptomatic and asymptomatic carotid stenosis, benefits of the two interventions have been consistently demonstrated for symptomatic moderate stenosis as well as asymptomatic severe stenosis albeit with lower benefit margin for asymptomatic disease. Intervention for asymptomatic carotid stenosis should only be considered when the complication rate can be maintained below 3%.

Keywords

Carotid Stenosis, Stenting

1. Introduction

The role of surgical carotid endarterectomy or endovascular stenting for carotid stenosis has been vigorously studied in multiple randomized trials over the past few decades. Results of the recently completed Second Asymptomatic Carotid Atherosclerosis Study (ACST-2) study have shed more light in the management of carotid stenosis [1]. This article represents a point of view from a neutral neurosurgeon who performs both surgery and endovascular treatment for carotid disease.

2. Main Text

For asymptomatic carotid stenosis more than 60% by North American Symptomatic Carotid Endarterectomy Trial (NASCET) [2] [3] criteria, carotid endarterectomy was proven to be superior to best medical therapy by Asymptomatic

Carotid Atherosclerosis Study (ACAS) [4] and Asymptomatic Carotid Surgery Trial (ACST-1) [5]. In ACAS trial, the aggregate risk of ipsilateral stroke over 5 years and any perioperative stroke or death was 11% with best medical therapy vs 5.1% in the surgical arm. For ACST-1, the equivalent event rates were 11.8% with best medical therapy vs 6.4% for surgical arm. The differences in outcome were statistically significant for both studies. In the ACST-2 study, which is a randomized trial of carotid endarterectomy vs stenting in severe asymptomatic carotid stenosis greater than 60% by NASCET criteria, 1% had disabling stroke or death procedurally (15 allocated to stenting and 18 to endarterectomy) and 2% had non-disabling procedural stroke (48 allocated to stenting and 29 to endarterectomy). Kaplan-Meier estimates of 5-year non-procedural stroke risks were 2.5% in each group for fatal or severe disabling stroke, and 5.3% with stenting versus 4.5% with endarterectomy for any stroke. The difference was statistically not significant and the study group concluded that "serious complications are similarly uncommon after competent stenting and endarterectomy, and the long term effects of these two carotid artery procedures on fatal or disabling stroke are comparable". The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial compared the role of stenting and endarterectomy in a group of high-risk patients [6] [7]. Patients were eligible for randomization to either endarterectomy surgery or carotid stenting with distal protection if they had at least one coexisting condition believed potentially to increase the risk posed by endarterectomy and if a study surgeon and interventionalist agreed patients could undergo either procedure safely. The inclusion criteria were the presence of one or more criteria for high surgical risk and a stenosis of more than 50% of the luminal diameter in patients with symptoms or a stenosis of more than 80% in those without symptoms. The criteria for high surgical risk were clinically significant cardiac disease (congestive heart failure, abnormal stress test or the need for open-heart surgery), severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, recurrent stenosis after carotid endarterectomy, previous radical neck surgery or radiation therapy to the neck or age of more than 80 years. Stenting was performed with the use of a self-expanding, nitinol stent (Smart or Precise, Cordis, USA) and an emboli-protection device (Angioguard or Angioguard XP Embolic Capture Guidewire, Cordis, USA). The 30-day major event (stroke, myocardia infarct or death) rate was 5.8% for the stenting group compared with 12.6% in the endarterectomy group. The durability of carotid stenting was also shown in this study. At 3 years follow-up, results showed that the prespecified end point (stroke, myocardia infarct or death) occurred in 41 patients in the stenting group (cumulative incidence, 24.6%; Kaplan-Meier estimate, 26.2%) and 45 patients in the endarterectomy group (cumulative incidence, 26.9%; Kaplan-Meier estimate, 30.3%). The investigators concluded that stenting was not inferior to endarterectomy and that no significant difference could be shown in the long-term outcomes between the two procedures.

Taken together, these four landmark randomized trials showed that there are two equally effective treatment options for asymptomatic severe carotid stenosis (>60% by NASCET criteria) if the periprocedural complication rate can be maintained below 3%, when the patient has a life expectancy of over 5 years.

The role of carotid endarterectomy in symptomatic carotid stenosis has been well established by randomised control trials. In patients with symptomatic atherosclerotic carotid stenosis greater than 70% by NASCET criteria, the value of endarterectomy was established by the results of NASCET and the European Carotid Surgery Trial (ECST) [8]. In NASCET, the estimate of any ipsilateral stroke at 2 years for patients with symptomatic high grade stenosis was 26% in the medical arm and 9% in the surgical arm. For symptomatic carotid stenosis in the moderate category (50% to 69% stenosis), NASCET and ECST demonstrated significant benefits for endarterectomy compared to best medical therapy. In NASCET, the 5-year risk of ipsilateral stroke over the 5-year follow period was 22.2% in the medically treated group compared to 15.7% in patients treated surgically. The surgical complication rate was kept below 6% in these trials. For patients with carotid stenosis below 50% by NASCET criteria, these trials showed that there was no significant benefit with surgery.

The first major randomised control trial for direct comparison of endarterectomy versus stenting was the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) [9]. In this study, three-quarters of the cases in endovascular group received balloon angioplasty alone without stenting. The rates of major outcome events within 30 days of first treatment did not differ significantly between endovascular treatment and surgery (6.4% vs 5.9%, respectively, for disabling stroke or death; 10.0% vs 9.9% for any stroke lasting more than 7 days, or death). Cranial neuropathy was reported in 22 (8.7%) surgery patients, but not after endovascular treatment ($p < 0.0001$). Major groin or neck haematoma occurred less often after endovascular treatment than after surgery (1.2% vs 6.7%, $p < 0.0015$). At 1 year after treatment, severe (70% - 99%) ipsilateral carotid stenosis was more common after endovascular treatment (14% vs 4%, $p < 0.001$). However, no substantial difference in the rate of ipsilateral stroke was noted with survival analysis up to 3 years after randomization. The investigators concluded that endovascular treatment had similar risks and effectiveness at prevention of stroke at three years compared with endarterectomy. They also concluded that there was a wide confidence interval and endovascular treatment had the advantage of avoiding minor complications. After the results were published the study was criticised for having too high a complication rate for the surgical arm and too much variation in the endovascular treatment arm in terms of acceptable techniques including with or without stenting or the use of distal protection. In the long term follow up study of the CAVATAS cohort the estimated cumulative 8-year incidence of non-perioperative ipsilateral stroke was 11.3% in the endovascular group and 8.6% in the endarterectomy group [10]. The overall risk difference was not significant when the data were analysed by intention-to-

treat or by treatment received.

Subsequent randomized control trials comparing endarterectomy vs stenting were more stringent in terms of requirements for operator experience as well as the devices used in the treatment arms. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) [11] trial compared stenting vs endarterectomy for patients with symptomatic carotid stenosis greater than 70% by NASCET criteria. For SPACE trial, surgeons must submit results for 25 consecutive endarterectomy procedures. Interventionist must have performed a minimum of 25 stenting or angioplasty procedures. Use of protection devices, predilation, and balloon was at the discretion of the interventional physician. In both the intention-to-treat and per-protocol analyses the Kaplan-Meier estimates of ipsilateral ischaemic strokes up to 2 years after the procedure and any periprocedural stroke or death did not differ between the carotid artery stenting and the carotid endarterectomy groups (intention to treat 9.5% vs 8.8%; $p = 0.31$). The investigators further reported that the incidence of recurrent carotid stenosis at 2 years, as defined by ultrasound, was significantly higher after carotid artery stenting. However, it could not be excluded that the degree of in-stent stenosis was slightly overestimated by conventional ultrasound criteria. In the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, the 30-day incidence of any stroke or death was 3.9% after endarterectomy and 9.6% after stenting [12] [13]. The 30-day incidence of stroke or deaths was 25% for stenting without distal protection compared with 7.9% with protection device. In fact, the study was temporarily stopped at one stage due to the excessive complication rate of stenting without distal protection. It is worth mentioning that in the EVA-3S trial, stents could be placed by physicians who had performed as few as five previous carotid-stent procedures or, if working under the direction of a tutor, with no previous procedural experience. There were five different stents and seven different distal protection devices used in various stages of the study. The cumulative probability of periprocedural stroke or death and non-procedural ipsilateral stroke after four years of follow-up was higher with stenting than with endarterectomy (11.1% vs 6.2%). A hazard function analysis showed that the 4-year differences in the cumulative probabilities of outcomes between stenting and endarterectomy were largely accounted for by the higher periprocedural (within 30 days of the procedure) risk of stenting compared with endarterectomy. After the periprocedural period, the risk of ipsilateral stroke was low and similar in both treatment groups. The cumulative probability of any ipsilateral stroke or procedural stroke/death at 5 years occurred in 11.0% of the stenting group vs. 6.3% of the endarterectomy group ($p = 0.04$), whereas the cumulative probability of any ipsilateral stroke or procedural stroke/death at 10 years occurred in 11.5% of the CAS group vs. 7.6% of the CEA group ($p = 0.07$). The trial investigators concluded that at 5 years of follow-up, there was an excess of any ipsilateral stroke or procedural stroke/death with stenting compared to endarterectomy. At 10 years, adverse events were

still numerically higher with stenting; however, the difference was nonsignificant. Postprocedural ipsilateral strokes were infrequent and occurred at a similar frequency between groups. On the contrary, in the SAPPHIRE trial, where high risk patients were randomized for stenting or endarterectomy, stenting was found not to be inferior to endarterectomy and that no significant difference could be shown in the long term outcomes between the two carotid interventional procedures. It is worth noting that in the SAPPHIRE trial, the selection of interventionist or surgeon was stringent. Surgical investigators had a median annual volume of 30 endarterectomies (range, 15 to 100). Because carotid-artery stenting was a relatively new procedure then, the total experience of interventional physicians with this procedure (median, 64 procedures; range, 20 to 700), instead of the annual volume, was reviewed by the study committee. In addition, only self-expanding, nitinol stent (Smart or Precise, Cordis, USA) and an emboli-protection device (Angioguard or Angioguard XP Embolic Capture Guidewire, Cordis, USA) was allowed. In the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST), where the outcomes of stenting with those of carotid endarterectomy among patients with symptomatic or asymptomatic extracranial carotid stenosis were compared, it was reported that for 2502 patients over a median follow-up period of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary end point between the stenting group and the endarterectomy group (7.2% and 6.8%, P = 0.51) [14]. The investigators further concluded that among patients with symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly in the group undergoing stenting and the group undergoing endarterectomy. During the periprocedural period, there was a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy. This trial was very stringent in the selection of surgeons for endarterectomy and interventionist for stenting. Certification was achieved by 477 surgeons, whose clinical results were audited by means of a validated selection process documenting that they performed more than 12 procedures per year and that the rates of complications and death were less than 3% among asymptomatic patients and less than 5% among symptomatic patients. The 224 interventionists were certified after satisfactory evaluation of their endovascular experience, carotid-stenting results, participation in hands-on training, and participation in a lead-in phase of training. For carotid-artery stenting, the protocol specified use of the RX Acculink stent (Abbott Vascular Solutions, IL, USA) and, whenever feasible, the RX Accunet embolic-protection device (Abbott Vascular Solutions, IL, USA). In the International Carotid Stenting Study (ICSS) the number of fatal or disabling strokes as well as cumulative 5-year risk did not differ significantly between the stenting and endarterectomy groups (6.4% vs 6.5%; p = 0.77) [15]. The investigators concluded that the long-term functional outcome and risk of fatal or disabling stroke are similar for stenting and endarterectomy for symptomatic carotid stenosis greater than 50%.

There have also been meta-analyses published based on the randomized trials and the conclusion appears to favour endarterectomy with a slightly higher complication risk of non-disabling strokes associated with carotid stenting [16]. The limitations of meta-analysis are well known. One of the major drawbacks of endovascular stenting is the myriad distal protection devices as well as stents used for the revascularisation procedures. Over the years various distal protection devices such as distal balloons, proximal or flow reversal protection balloons, filter wires, etc, have been developed with variable results. Different types of stents including balloon mounted stents, self-expanding stents, closed cell stents, open cell stents, tapered stents and even covered stents have been used at various stages in the past. Therefore, the results of the separate trials with or without distal protection devices as well as different devices may not be comparable. It appears that with prior training and the use of specific distal protection devices and stents as in SAPPHIRE and CREST trials, complications with carotid stenting could be reduced and no significant difference could be detected in long term follow up studies comparing stenting vs endarterectomy.

Without going into complex statistical analysis, it is obvious that in objective randomized clinical trial settings, the long-term outcome for carotid endarterectomy or stenting is similar and ranged roughly from around 3% to 12% for composite event rates of disabling stroke, myocardial infarction or death. Some of the trials mentioned above included over thousand cases with follow up long term to ten years. With a large enough sample size, the treatment arm with a lower complication rate will emerge as the better treatment option. There will always be criticisms for any randomized trial designs. The proponents of either treatment options will not be satisfied when the results go against their expectation. No one can deny the fact that both therapeutic options require proper training and experience to achieve low complication rates. There are as many nuances in carotid stenting as in endarterectomy to avoid perioperative morbidities.

3. Conclusion

In conclusion, randomized trials so far support both endarterectomy and stenting as effective treatments for symptomatic carotid stenosis above 50% and asymptomatic stenosis above 60% if the perioperative complication rate can be maintained at a low level. Intervention for asymptomatic carotid stenosis should only be considered when the complication rate can be maintained below 3%.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Value of Real-Time Bedside Ultrasonography in the Etiologic Diagnosis of Acute Dyspnea

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Abstract

Objective: To explore the value of real-time bedside ultrasonography in the etiologic diagnosis of acute dyspnea. **Methods:** Sixty-two patients with acute dyspnea who were treated in our hospital from January 2016 to December 2020 were randomly selected and their clinical data were retrospectively analyzed. All patients were randomly divided into a control group for routine examinations (n = 31) and an observation group for real-time beside ultrasonography (n = 31). The costs of medical examinations, examination duration, and diagnostic results of severe pneumonia, acute cardiogenic pulmonary edema, pulmonary embolism, chronic obstructive pulmonary disease, and pneumothorax (including sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy) of the two groups of patients were compared and analyzed. **Results:** Compared with the control group, the observation group had significantly shorter examinations ($P < 0.05$). Although the cost of medical examinations of the observation group tended to be higher, the difference between groups was not significant ($P > 0.05$). Moreover, there were no significant differences in left ventricular ejection fraction, left ventricular end-diastolic diameter, or brain natriuretic peptide between the two groups ($P > 0.05$). Comparison of the etiologic diagnosis results between the two groups showed that the observation group had significantly higher diagnostic sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy for various causes compared with the control group ($P < 0.05$). **Conclusion:** Real-time bedside ultrasonography for the etiologic diagnosis of patients with acute dyspnea was quicker and had higher diagnostic accuracy; thus providing accurate guidance for the disease treatment, and having a higher promotional value in clinical practice compared with routine examinations.

Keywords

Real-Time Bedside Ultrasonography, Acute Dyspnea, Etiological Diagnosis,

Clinical Diagnosis

1. Introduction

Dyspnea is relatively common in clinical practice, especially in critically ill patients in emergency departments. Dyspnea triggers many factors, including toxicity, hematogenous, cardiogenic, pulmonary, and neuropsychiatric factors. Dyspnea in patients who fail to receive timely and effective treatment are gradually aggravated with prolonged treatment, often leading to death in a short time. Hence, timely and accurate evaluation of the disease is key to the successful treatment of patients with dyspnea and the formation of corresponding treatment regimens based on the evaluation results [1]. Computed tomography (CT), biochemical blood tests, and X-ray examinations are common methods for the diagnosis and detection of the causes of acute dyspnea. Despite their relatively good diagnostic efficacy, these methods cannot be conducted at the bedside, especially during the process of hospital transferring and examinations of the patients [2]. With the continuous development of clinical diagnostic technology and the continuous updating and application of diagnostic equipment in China, bedside ultrasonography has been extensively used in the etiological diagnosis of acute dyspnea patients in clinical practice, and its effects have been highly recognized by both medical professionals and patients [3]. Real-time bedside ultrasonography facilitates faster, simpler, and more accurate diagnosis, helping clinicians to quickly analyze the causes of patient's illness. Real-time bedside ultrasonography is a noninvasive examination that can monitor a patient's conditions in real time without causing radiation damage to the patient [4]. In the current study, we selected patients with acute dyspnea who were treated in our hospital in the past 3 years, retrospectively analyzed their clinical data, and listed the diagnostic value of real-time beside ultrasonography on the causes of acute dyspnea.

2. Information and Methods

2.1. General Information of the Patients

Sixty-two patients with acute dyspnea who were treated in our hospital from January 2016 to December 2020 were randomly selected and their clinical data were retrospectively analyzed. The inclusion criteria were as follows: 1) patients who met the diagnostic criteria of acute dyspnea [5] and were confirmed to have acute dyspnea; 2) patients with complete clinical data; and 3) patients whose family members were informed of this study. The exclusion criteria of this study were as follows: 1) patients with contraindications to real-time bedside ultrasonography for the diagnosis; 2) patients with severe infectious diseases; and 3) with mental illness. All patients were randomly divided into a control group (n = 31) and an observation group (n = 31). The observation group comprised 21

males and 10 females, with the youngest age of 27 years old and the oldest age of 68 years old (mean age: 55.38 ± 5.81 years old). Among the patients of the observation group, 4 patients had acute cardiogenic pulmonary edema, 8 patients had severe pneumonia, 8 patients had chronic obstructive pulmonary disease, 5 patients had pulmonary embolism, and 6 patients had pneumothorax. The control group comprised 22 males and 9 females, with the youngest age of 28 years old and the oldest age of 28 years old (mean age: 55.08 ± 5.01 years old). Among the control group, 5 patients had acute cardiogenic pulmonary edema, 9 patients had severe pneumonia, 8 patients had chronic obstructive pulmonary disease, 4 patients had pulmonary embolism, and 5 patients had pneumothorax. The research protocol of this study was approved by the ethics committee of our hospital. No significant difference in general information was found between the two groups ($P > 0.05$).

2.2. Methods

The diagnostic criteria of dyspnea included abnormal changes in the heart shadow in X-ray, rales at the bottom of the lungs, and a significant change in pulmonary rales when changing the body position of the patients. The severity of dyspnea was based on the degrees of damage during gas exchange and the breathing pattern of the patients.

The control group received routine examinations, including chest X-ray, measurement of brain natriuretic peptide (BNP), analysis of arterial blood gas, various physical examinations, troponin (TNI) test, and routine blood tests. A comprehensive analysis based on the results of each examination was performed by physicians of each department before preparing the corresponding treatment regimens for individual patients. Elbow venous blood (5 ml) was collected from each patient and placed in a collecting tube containing ethylenediaminetetraacetic acid (EDTA) anticoagulant. The blood sample was centrifuged at 3000 rpm for 15 min before collecting the serum to detect BNP by enzyme-linked immunosorbent assay. The left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVED) of the patients were detected by conventional electrocardiogram before recording the details.

The observation group received real-time bedside ultrasonography. In brief, a color Doppler ultrasound diagnostic apparatus (Kaili portable color Doppler Elexp) and its matching three-dimensional ultrasound probes, 4 V and MSS probes, were used for lung ultrasonography by adjusting the frequency of the 4 V and MSS probes to 1.5 MHz - 4.0 MHz and 2.0 MHz - 4.0 MHz in each patient in the supine position. Lung ultrasonography was conducted by a physicians who did not participate in the diagnosis and treatment of the patient. The results were analyzed by the attending physician to devise the appropriate treatment regimens for each patient. The BNP level was detected by a rapid beside test for BNP, and the LVEF and LEVD were measured by real-time bedside ultrasonography before recording the details.

2.3. Observation Indicators

The costs of the medical examinations; the examination duration; the diagnostic results of severe pneumonia, acute cardiogenic pulmonary edema, pulmonary embolism, chronic obstructive pulmonary disease, and pneumothorax (including sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy); and the LVEF, LVED, and BNP of the patients in the two groups were recorded and statistically analyzed. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were determined using the following equations:

Sensitivity = number of true positive cases/(number of true positive cases + number of false negative cases) × 100%

Specificity = number of true negative cases/(number of true negative cases + number of false positive cases) × 100%

Negative predictive value = number of true negative cases/(number of true negative cases + number of false negative cases) × 100%

Positive predictive value = number of true positive cases/(number of true positive cases + number of false positive cases) × 100%

Accuracy rate = (number of true positive cases + number of true negative cases)/total number of patients × 100%.

2.4. Statistical Analysis

The SPSS 20.0 software package (IBM, Armonk, NY) was used to perform all statistical analyses. The results of the examination duration, cost of medical examinations, and levels of LVEF, LVED, and BNP are presented as ($\overline{x} \pm s$), and a t-test was used to compare the differences between the groups. The sensitivity, specificity, positive predictive value, negative predictive value, and the rate of diagnostic accuracy are presented as (n, %), and the chi-square test was used to compare the differences between the two groups. A P-value < 0.05 was considered to indicate a significant difference.

3. Results

3.1. Examination Duration and Costs of Medical Examinations

Comparison of the examination duration between the two groups showed that the duration of examination in the control group (46.89 ± 5.82 min) was significantly longer than that of the observation group (19.21 ± 2.65 min) (P < 0.05). Although the cost of medical examination in the observation group (CN¥785.05 ± 8.05) tended to be higher than that of the control group (CN¥781.00 ± 7.03), no significant difference was found between the two groups (P > 0.05, see Table 1 for details).

3.2. LVEF, LVED, and BNP Levels

As shown in Table 2, no significant differences in the levels of LVEF, LVED, or BNP were found between the two groups of patients.

Table 1. Comparison of the examination duration and cost of medical examinations between the two groups.

Group	Examination duration (min)	Cost of medical examination (CN¥)
Observation group (n = 31)	19.21 ± 2.65	785.05 ± 8.05
Control group (n = 31)	46.89 ± 5.82	781.00 ± 7.03
T	13.841	2.346
P	<0.001	0.047

Table 2. Comparison of LVEF, LVE, and BNP levels between the two groups.

Group	LVEF (%)	LVED (m)	BNP (ng/L)
Observation group (n = 31)	48.21 ± 5.65	57.05 ± 5.25	275.33 ± 54.25
Control group (n = 31)	47.89 ± 5.82	56.34 ± 5.64	278.34 ± 55.64
t	1.041	1.146	1.384
P	0.102	0.113	0.135

3.3. Results of Etiologic Diagnosis in the Two Groups

As shown in Tables 3-7, comparison of the diagnostic results of the two groups showed that the observation group had higher diagnostic sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy for various causes of acute dyspnea than the control group ($P < 0.05$).

4. Discussion

Dyspnea is relatively common in clinical practice, especially in the emergency department, and represents one of the main complaints of critically ill patients. With the gradual increase in the clinical research, data have shown that more than 20 million patients in the emergency department complain of respiratory tract dysfunction annually. Moreover, patients who present to the emergency department with dyspnea as the main complaint account for approximately 5% of the total number of patients in the emergency department [6]. Continuous improvement and optimization of existing diagnoses and treatment regimens greatly reduce the mortality of patients with acute dyspnea. X-ray and CT are commonly used for the etiologic diagnosis of acute dyspnea. Although X-ray diagnosis can be performed at the bedside, the value of imaging data obtained is relatively low and does not support the whole process of diagnosis and treatment, resulting in limited application [7]. Although the imaging data obtained by CT for the diagnosis are relatively abundant, CT cannot be performed at the bedside and requires patients to be transferred from the ward to the CT room for the examination and then transferred back from the CT room to the ward. The transportation of patients for CT and back is extremely risky for critically ill patients [8].

Recently, with the continuous development of ultrasound diagnostic technology and the continuous updating and upgrading of ultrasound diagnostic equipment

Table 3. Comparison of the diagnostic results of severe pneumonia based on the two diagnostic methods (%).

Group	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
Observation group (n = 8)	87.50 (7/8)	40.00 (2/5)	77.78 (7/9)	80.00 (4/5)	69.23 (9/13)
Control group (n = 9)	62.50 (5/8)	20.00 (1/5)	55.56 (5/9)	40.00 (2/5)	46.15 (6/13)
χ^2	9.045	9.684	10.684	19.557	11.531
P	<0.001	<0.001	<0.001	<0.001	<0.001

Table 4. Comparison of the diagnostic results of acute cardiogenic pulmonary edema based on the two diagnostic methods.

Group	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
Observation group (n = 4)	60.00 (3/5)	66.67 (2/3)	60.00 (3/5)	75.00 (3/4)	62.50 (5/8)
Control group (n = 5)	40.00 (2/5)	33.33 (1/3)	40.00 (2/5)	50.00 (2/4)	37.50 (3/8)
χ^2	8.066	12.012	9.043	12.005	12.981
P	0.005	<0.001	<0.001	<0.001	<0.001

Table 5. Comparison of the diagnostic results of pulmonary embolism based on the two diagnostic methods.

Group	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
Observation group (n = 5)	66.67 (4/6)	66.67 (2/3)	71.43 (5/7)	60.00 (3/5)	66.67 (6/9)
Control group (n = 4)	33.33 (2/6)	33.33 (1/3)	28.57 (2/7)	40.00 (2/5)	33.33 (3/9)
χ^2	12.012	12.012	20.091	9.842	12.012
P	<0.001	<0.001	<0.001	<0.001	<0.001

Table 6. Comparison of the diagnostic results of chronic obstructive pulmonary disease based on the two diagnostic methods.

Group	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
Observation group (n = 8)	70.00 (7/10)	50.00 (2/4)	88.89 (8/9)	66.67 (4/6)	64.29 (9/14)
Control group (n = 8)	40.00 (4/10)	25.00 (1/4)	55.56 (5/9)	33.33 (2/6)	35.71 (5/14)
χ^2	14.871	12.092	15.872	12.012	14.831
P	<0.001	<0.001	<0.001	<0.001	<0.001

Table 7. Comparison of the diagnostic results of pneumothorax based on the two diagnostic methods.

Group	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
Observation group (n = 6)	71.43 (5/7)	66.67 (2/3)	77.78 (7/9)	60.00 (3/5)	60.00 (6/10)
Control group (n = 5)	42.86 (3/7)	33.33 (1/3)	44.44 (4/9)	40.00 (2/5)	30.00 (3/10)
χ^2	14.761	12.012	16.982	9.631	14.779
P	<0.001	<0.001	<0.001	<0.001	<0.001

in China, real-time bedside ultrasonography has been extensively used in the diagnosis of patients with acute dyspnea, especially in the etiologic analysis and diagnosis, with good results [9]. Real-time bedside ultrasonography is not only rapid in terms of diagnosis, but also simple in operation. Moreover, real-time

bedside ultrasonography can be used to acquire a high accuracy rate on imaging data, providing important guidance for the clinical diagnosis and treatment of acute dyspnea [10]. Real-time bedside ultrasonography also reveals the conditions of the respiratory tract in real-time, facilitating the rapid identification of the cause of dyspnea and the ability to formulate accurate treatment regimens, thereby improving the survival of the patients [11]. In this study, the examination duration of patients receiving real-time bedside ultrasonography was 19.21 ± 2.65 min, which was significantly shorter than that of routine examinations (46.89 ± 5.82 min, $P < 0.05$). Although the cost of medical examination via real-time bedside ultrasonography (CN¥785.05 ± 8.05) was higher than that of routine examinations (CN¥781.00 ± 7.03), no significant difference was found between the two diagnostic methods. A study of Gu *et al.* [12] also showed that the examination duration of patients who received real-time bedside ultrasonography (19.31 ± 3.98 min) was significantly shorter than that of patients who received routine examinations (55.89 ± 4.96 min). Similarly, in the same study, the cost of medical examination of the real-time bedside ultrasonography (CN¥786.75 ± 8.36) was higher than that of the routine examinations (CN¥783.51 ± 9.88), while no significant difference in cost was found between the two diagnostic methods, which is consistent with our findings. These results suggest that real-time bedside ultrasonography for the diagnosis of acute dyspnea provides accurate guidance for the analysis of etiologies, accelerated the etiological diagnosis, and facilitated early treatment of the patients.

BNP is a type of neurohormone in the heart, which is mainly secreted by atrial and ventricular cardiomyocytes. Under normal circumstances, when the heart pressure is overloaded, and the blood volume of the heart continues to increase, the ventricular cardiomyocytes will secrete a high level of BNP, which not only has a diuretic effect, but also promotes the dilation of blood vessels, inhibits the activity of the sympathetic nerve system and the renin-angiotensin-aldosterone system, and effectively promotes the proliferation of endothelial cells. Changes in BNP levels accurately reflect changes in ventricular function, as do levels of LVEF and LVED. Some researchers have shown that the higher the BNP level and the lower the LVEF, the more severe the dyspnea. Moreover, BNP is an important hemodynamic index that accurately reflects the left ventricular end-diastolic pressure and provides a basis for relatively accurate clinical diagnosis of acute dyspnea [13]. The results of the current study showed no significant differences in LVEF, LVED, or BNP levels between the two diagnostic methods, which may be due to the relatively small number of patients included in this study.

Additionally, in terms of diagnostic results, real-time bedside ultrasonography had significantly higher diagnostic sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy for various causes of acute dyspnea compared to routine examinations ($P < 0.05$). The study of Sun *et al.* [14] also showed that real-time bedside ultrasonography had significantly higher diagnostic sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy for various causes of acute dyspnea compared to

routine examinations ($P < 0.05$). These findings are consistent with our findings and further confirm that real-time bedside ultrasonography has both high sensitivity and specificity for the etiologic diagnosis of acute dyspnea. We also noted that pneumonia caused significant changes in the subpleural nodules and pleura, resulting in some signs of consolidation in the lungs, such as anechoic areas in the chest, hepatization, and shred sign. These tiny lesions are difficult to capture by conventional X-ray examination [15]; however, real-time bedside ultrasonography accurately captured the information on these tiny lesions and provided accurate guidance for disease diagnosis [16]. After the onset of pulmonary embolism, pulmonary artery become widened, pulmonary artery pressure is increased, and the volume of the right ventricle is increased. The information obtained by conventional X-ray examination is limited, but real-time bedside ultrasonography reveals the indicators of pulmonary function in real time. The information obtained from real-time bedside ultrasonography is more comprehensive, assisting the accurate diagnosis of pulmonary embolism [17]. After the onset of acute cardiogenic pulmonary edema, the systolic function of the left ventricle is weakened, increasing the left ventricular end-diastolic pressure, which frequently leads to complications, including pulmonary congestion and pulmonary edema. The adoption of convention examination requires a relatively long waiting time, and the accuracy of the diagnosis is not guaranteed. The implementation of real-time bedside ultrasonography can continuously scan and diagnose the lateral and anterior chest walls of patients with cardiogenic dyspnea. Moreover, images obtained using real-time bedside ultrasonography show a gravity-dependent bilateral and uniform distribution of B-lines. Under normal circumstances, the conditions of patients who fail to receive timely and effective treatment after the disease onset gradually worsen with time, and the density of B-lines distributed in the images increases [18]. Clinical research has shown that real-time bedside ultrasonography can also be used to analyze the influencing factors of the hemodynamics of some patients with acute dyspnea to provide supportive information for clinical diagnosis [19]. For example, information on ventricular wall thickening, slender inferior vena cava, systolic and diastolic function, and heart chamber size may assist a more accurate determination of the etiology and avoid the challenge of follow-up treatment or other adverse events caused by inaccurate diagnosis of the etiology [20].

5. Conclusion

In conclusion, the application of real-time bedside ultrasonography for the etiologic diagnosis of acute dyspnea required a shorter examination duration and achieved a higher diagnostic accuracy, providing accurate guidance for the clinical treatment of acute dyspnea. Therefore, we suggest a more frequent application of this technique in the clinic.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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A Comparison of Five Adhesive Tapes for Securing Endotracheal Tube in a Manikin

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Abstract

Background: Adhesive tape is the common method for endotracheal tube (ETT) secured to prevent tube displacement and unplanned extubation in an anesthesia setting. However, it is unclear which tape is superior for ETT fixation among the various tapes used in clinical practice. This study examines the force required to move 2 cm ETT and extubate ETT from an intubation manikin with five different adhesive tapes. **Methods:** We orally intubated an adult intubation manikin with an inner-diameter 7.5 mm ETT, inflated the cuff to 20 cm H_2O. Then we secured ETT with five different adhesive tapes (Transpore tape™, Urgosyval tape®, Transpore™ White tape, Multipore tape, Durapore™ tape) in a conventional fixation method. A digital force gauge was connected to the ETT and pulled in a direction erected to the oral cavity. We measured the force required to move 2 cm ETT and extubate ETT (defined as 5 cm ETT displacement) from the manikin. Data were analyzed with one-way analysis of variance, with $P < 0.05$. **Results:** Durapore™ tape had the largest average force of 2 cm displacement (58.9 ± 5.7N) ($P < 0.05$). The extubation force of Durapore™ tape (59.7 ± 4.9N) was larger than Urgosyval® tape (40.4 ± 2.9N) ($P < 0.05$), Transpore™ tape (48.7 ± 5.1N) ($P < 0.05$), Transpore White™ tape (48.7 ± 5.1N) ($P < 0.05$). **Conclusion:** Durapore™ tape was superior to the other four tapes (Transpore™ tape, Urgosyval® tape, Transpore™ white tape, Multipore tape) in holding the ETT in place in the manikin.

Keywords

Adhesive Tape, Extubation Force, Endotracheal Tube Fixation, Manikin

1. Introduction

Adequate endotracheal tube (ETT) fixation in an intubation patient is essential to prevent potentially life-threatening complications. During the general anes-

thesia, ETT displacement or accidental extubation may occur at any time for various reasons. ETT displacement or accidental extubation may occur when a patient is being transported [1]. It may happen when the surgeon requires frequent movement of head or neck to exposure certain surgery site [2].

ETT displacement or accidental extubation may lead to atelectasis formation, vocal cord injury, aspiration, respiratory arrest, hypoxemia, hypotension, cardiac arrest, anoxic brain injury, or even death [3] [4] [5] [6] [7]. Hence, the fixation of ETT is of utmost importance as not only provides effective ventilation but also minimizes complications due to accidental extubation.

Many devices and techniques to secure ETT are in use, including tape, ETT holders, twill, sucture, etc. Comparisons of adhesive tape versus ETT holder have not demonstrated that either is superior [8]-[14]. Tape is primarily used in the operating room at our institution. However, it is unclear which tape is superior for ETT fixation among the various tapes used in clinical practice. In the work, we usually choose the strong adhesion, good material, not easy to rip, and economical adhesive tape to secure ETT. But few studies are comparing different types of tapes used for ETT fixation.

The purpose of this study was to evaluate the force of ETT displacement or extubation when tapes of five different materials were applied for ETT fixation on a manikin.

2. Materials and Methods

An adult intubation manikin (Ambu, China) was orally intubated by one of the investigators using a standing intubation technique that included spraying medical lubricating fluid. An inner-diameter 7.5 mm ETT (wellead®, Well Lead Medical co., LTD. Guangzhou, China) was inserted to 23 cm away from the manikin lower incisors. The cuff of ETT was inflated to a pressure of 20 cm H_2O. Then a marker was made on the ETT just external to the manikin lower incisor to observe the displacement distance of ETT.

The ETT was secured with five different adhesive tapes used in our institution. **Figure 1** shows the five different adhesive tapes. The material and brand of the five tapes in the work are listed in **Table 1**. All five types of tapes were split into the same dimensions (length 25 cm, width 1.25 cm), then they adhered to the ETT around the manikin cheek in random order with a conventional fixation method shown in **Figure 2**.

A digital push-pull force gauge (ELECALL, ELK-300, China) accurate to 0.1 Newton was attached to the proximal end of the ETT. A gradually escalating force perpendicular to the oral cavity of the manikin was applied by one of the investigators. At the same time, another investigator stabilized the manikin head to prevent movement. The digital force gauge stored the maximum force at 2 cm displacement and extubation. Extubation was defined as 5 cm ETT displacement. Each tape was tested 5 times. Intubation, ETT fixation, the observation of ETT displacement distance, and the holding manikin head were performed by

Table 1. The material and brand of the five adhesive tapes used for endotracheal tube fixation in our institution.

	Type of tape	Material	Brand and manufacturer
Tape 1	Transpore™ tape	Polyethylene adhesive tape	Transpore™, 3M
Tape 2	Urgosyval® tape	Silk adhesive tape	Urgosyval®, Urgo Healthcare Products Co., Ltd. Thailand
Tape 3	Transpore™ White tape	Non-woven fabric adhesive tape	Transpore™ White, 3M
Tape 4	Multipore tape	Cotton elastic adhesive tape	Multipore, 3M, Japan
Tape 5	Durapore™ tape	Silk adhesive tape	Durapore™, 3M

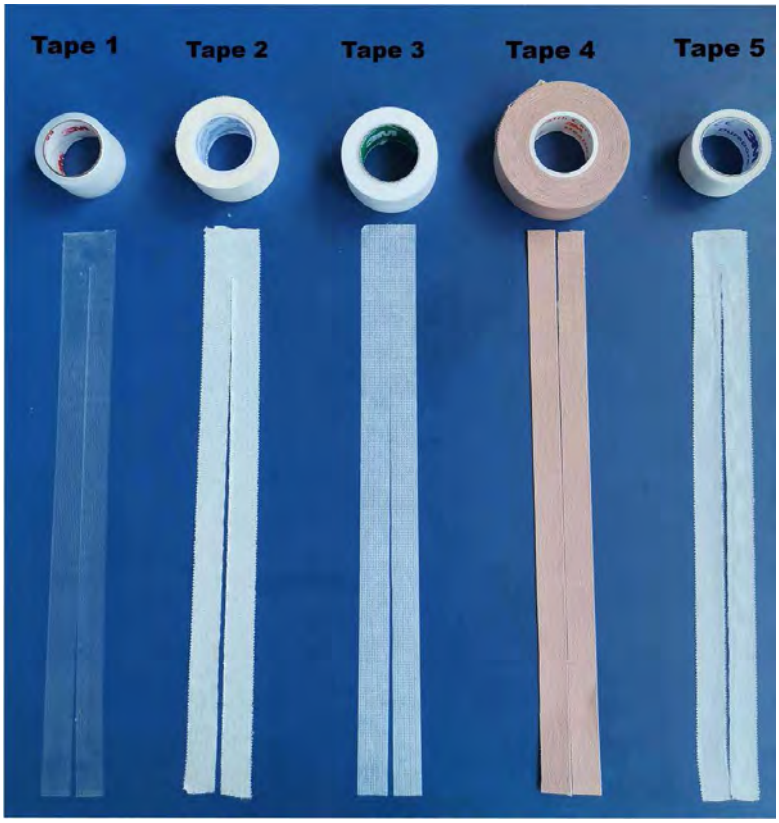


Figure 1. Five different adhesive tapes used for endotracheal tube fixation in our institution. The tapes were split into the same dimensions (length 25 cm, width 1.25 cm). Tape 1: Transpore™ tape, Tape 2: Urgosyval® tape, Tape 3: Transpore™ White tape, Tape 4: Multipore tape, Tape 5: Durapore™ tape.

the same researcher. The implementation of pulling force and recording the maximum force values were done by another researcher. A new ETT and tape were used for every test. During 2 cm displacement and extubation, we recorded the tape rip or not, and the adhesive state included partial or complete peeling off the surface of manikin. We also compared the cost per test of each tape to know their cost-effectiveness.

The parameters with normal distribution were expressed as mean ± standard deviation (SD) and 95% confidence interval (CI). The difference of force values

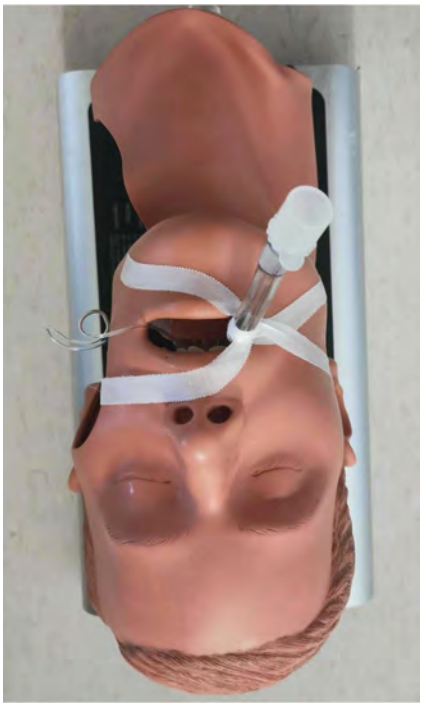


Figure 2. The conventional fixation method of endotracheal tube with tape on the manikin.

among five different tapes was assessed with one-way analysis of variance and that between groups with Bonferroni test. Statistical analysis was performed by SPSS 16.0 (SPSS Inc., USA). For all analyses, two-tailed *P* value of less than 0.05 were considered statistically significant.

Tape was split into the same dimensions (length 25 cm, width 1.25 cm), One of them was attached to one side of the cheek, wrapped around the ETT two circles, and then cross-fixed on the same side of the cheek, and the other tape was wrapped around the ETT two circles and fixed along the upper and lower lips.

3. Results

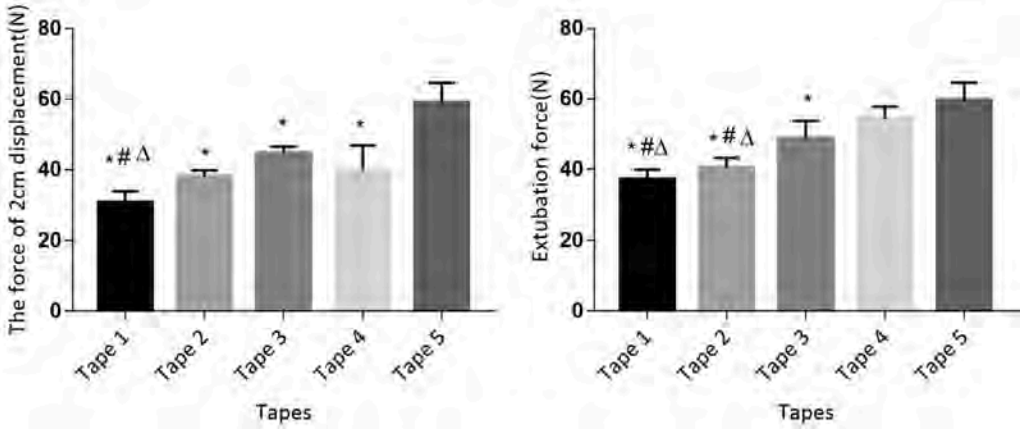
Table 2 shows the force values of 2 cm ETT displacement and extubation with five different adhesive tapes. The force was significantly difference among the five tapes in 2 cm ETT displacement ($P < 0.05$). Similarly, the extubation force was significantly different ($P < 0.05$). The results of Bonferroni test between groups are shown in **Figure 3**. Durapore™ tape (Tape 5) had the largest average force of 2 cm displacement (58.9 ± 5.7N). The extubation force of Durapore™ tape was larger than Urgosyval® tape ($P < 0.05$), Transpore™ tape ($P < 0.05$), Transpore™ White tape ($P < 0.05$). Whereas, the extubation force of Durapore™ tape (Tape 5) and Multipore tape (Tape 4) had no significant difference.

Table 3 shows the integrity of tapes and the adhesive state of the tape-manikin interface when the ETT was moved to 2 cm or extubated. Urgosyval® tapes were completely peeling off surface of the manikin. Transpore™ tape and Transpore™ White tape were ripped.

Table 2. The force of five different adhesive tapes at 2 cm ETT displacement and extubation (N).

	Force of 2 cm displacement			Extubation force		
	mean ± SD	95% CI		mean ± SD	95% CI	
		lower	upper		lower	upper
Tape 1	30.6 ± 3.2	33.7	40.6	37.1 ± 2.8	26.6	34.6
Tape 2	37.9 ± 1.9	36.9	43.9	40.4 ± 2.9	35.6	40.2
Tape 3	44.6 ± 1.9	42.4	55.0	48.7 ± 5.1	42.2	47.0
Tape 4	40.0 ± 6.8	50.3	58.5	54.4 ± 3.3	31.6	48.5
Tape 5	58.9 ± 5.7	53.6	65.7	59.7 ± 4.9	51.9	65.9

Tape 1: Transpore™ tape, Tape 2: Urgosyval® tape, Tape 3: Transpore™ White tape, Tape 4: Multipore tape, Tape 5: Durapore™ tape. ETT: endotacheal tube, SD: standard deviation, CI: confidence interval.



(a) (b)

Figure 3. Comparisons of the force of 2 cm displacement and extubation force between different tapes used for endotracheal tube fixation on a manikin. Tape 1: Transpore™ tape, Tape 2: Urgosyval® tape, Tape 3: Transpore™ White tape, Tape 4: Multipore tape, Tape 5: Durapore™ tape. $^{*}P < 0.05$ compared to Tape 5; $^{\#}P < 0.05$ compared to Tape 4; $^{\Delta}P < 0.05$ compared to Tape 3.

Table 3. Tape integrity and adhesive state of tape-manikin interface at 2 cm ETT displacement and extubation.

	2 cm displacement					extubation				
	Tape1	Tape2	Tape3	Tape4	Tape5	Tape1	Tape2	Tape3	Tape4	Tape5
Partial peeling off the surface	−	−	−	−	+	−	−	−	+	+
complete peeling off the surface	−	+	−	−	−	−	+	−	−	−
Tape ripped	+	−	+	−	−	+	−	+	−	−

+: the event occurred, −: the event did not occur. Tape 1: Transpore™ tape, Tape 2: Urgosyval® tape, Tape 3: Transpore™ White tape, Tape 4: Multipore tape, Tape 5: Durapore™ tape, ETT: endotracheal tube.

Cost per test for 2 strips of 1.25 cm × 25 cm dimensions were ¥0.55, 0.77, 0.33, 2.45 and 0.55 for tapes from Tape 1 to Tape 5, respectively. Thus, Multipore tape (Tape 4) was the costliest and Transpore™ White (Tape 3) tape cheapest (**Table 4**).

Table 4. Comparative cost analysis of the five different tapes.

Tapes	CNY/per test(¥)*+
Tape 1	0.55
Tape 2	0.77
Tape 3	0.33
Tape 4	2.45
Tape 5	0.55

*Cost per test = 2 strips of 1.25 cm × 25 cm dimension. +Cost as per our institution store prices. Tape 1: Transpore™ tape, Tape 2: Urgosyval® tape, Tape 3: Transpore™ White tape, Tape 4: Multipore tape, Tape 5: Durapore™ tape.

4. Discussion

We compared the force values of 2 cm ETT displacement and extubation among five different tapes used for ETT fixation on an adult intubation manikin, the results demonstrated that Durapore™ tape was superior to the other four tapes for ETT fixation. In addition, Durapore™ tape may widely been used in the operating room because it is economical.

Securing ETT is critical for intraoperative airway management. Unplanned extubation or ETT displacement can cause serious complications, including death. Currently, the most widely used method is adhesive tape [6] [15]. Our results shown the force of 2 cm ETT displacement for Durapore™ tape was 58.9 ± 5.7N, extubation force was 59.7 ± 4.9N. Similarly, Shimizu *et al.* tested 3 brands of tape (Durapore™, Multipore Dry, and Wardel) in a manikin, the results shown extubation force of Durapore™ tape in 1.3 × 10 cm dimension were 49 ± 5N [9]. Another study comparing seven tube fixation methods on a laerdal intubation mannequin shown the force values of adhesive tape in 2 cm and 5 cm ETT displacement were 85 ± 26N and 144 ± 21N [16]. The possible reason that the force was greater than our results was that Lillehei method used in their study created a stabilization harness around the head of mannequin. While the Lillehei method seems unsuitable for all intubated patients with general anesthesia because it takes time to prepare and place the tape [11]. In clinical anesthesia, Lillehei method is rarely used to secure ETT. Similar to Shimizu's research [9], we used a conventional fixation method, which was more consistent with clinical routine.

We observed few differences between the force of 2 cm displacement and extubation force. It may be the lack of elasticity on the surface of the manikin, so a large force was required to cause 2 cm displacement. At the same time, the great force had caused tapes to peel off the surface of the manikin or rip. When tapes had lost their integrity and adhesiveness before extubation, force could not increase.

The extubation force of Multipore tape and Durapore™ tape were 54.4 ± 3.3N and 59.7 ± 4.9N, respectively. The difference was not statistically significant. However, the force of Durapore™ tape was larger than that of Multipore tape in 2 cm displacement ($P < 0.05$). Since the Multipore tape is a cotton elastic adhe-

sive tape, we speculate that a small force may cause 2 cm displacement due to its elasticity. Therefore, the effect of Durapore™ tape to secure ETT is better than Multipore tape.

Our study had several limitations. First, the manikin surface cannot match the structural properties of the human skin surface completely. Second, certain factors encountered in clinical practice, such as vomit, facial grease, disinfectant, beards, and oral secretions were not mimicked in our simulation. So the effect of these tapes on real cases needs to be confirmed by clinical trials. Third, the force we applied to ETT was in the same direction, whereas the force encountered during the operation with general anesthesia may be multidirectional and rapidly changing. Furthermore, we only measured the force of a single dimension of the tapes, whereas increasing the width and length of the tape may increase the force of displacement and extubation. Finally, head rotation is also a potential cause of extubation or displacement, but we limited the manikin head in anatomic position.

5. Conclusion

In conclusion, Durapore™ tape used for ETT fixation on the manikin is superior to the other four tapes (Transpore™ tape, Urgosyval tape®, Transpore™ White tape, Multipore tape), and it is economical. The effect of different adhesive tapes on patients needs to be confirmed by clinical trials.

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Authors' Contributions

Sanqing Jin designed the study and supervised the whole process of the study and revised the manuscript. Dongxue Li and Xia Huang collected and analyzed the data, and Dongxue Li wrote the manuscript.

Conflicts of Interest

All authors have no interests to be declared.

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