Application of Multiparameter Diffusion Weighted Imaging of In Vitro Scanning Pleural Effusion in Different Diseases

Yang Honglei

The Graduate School

Yonsei University

Department of Medicine

Application of Multiparameter Diffusion Weighted Imaging of In Vitro Scanning Pleural Effusion in Different Diseases

Instructed by Prof. Sung-Min Ko

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This certifies that the Master's Thesis of

Yang Honglei is approved

Sung-Min Ko

Professor Sung-Min Ko: Thesis Instructor

Sang-Ha Kim

Professor Sang-Ha Kim: Committee Member

Won-Yeon Lee

Professor Won-Yeon Lee: Committee Member

The Graduate School

Yonsei University

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ABSTRACT

Application of Multiparameter Diffusion Weighted Imaging of In Vitro Scanning Pleural Effusion in Different Diseases

Yang Honglei

Department of Medicine

The Graduate School, Yonsei University

Instructed by Professor Sung-Min Ko

Objectives: A preliminary study to evaluate the sequential alterations of the apparent diffusion coefficients (ADC) values of pleural effusions using in vitro magnetic resonance diffusion-weighted imaging.

Materials and methods: Fifteen pleural effusions (3 chronic renal insufficiency, 4 infection, 4 malignancy, 4 trauma) were included in this prospective study. Single-shot echo-planar spin-echo DWI using 3 Tesla MRI was performed with three b factors (500,

1000, and 2000 s/mm^2) and the ADC values of aspirated pleural fluids were measured immediately, 2 and 4 weeks at the ADC map.

Results: The initial ADCs of the traumatic effusions were significantly lower than the others (1.62±1.25×10-3mm^2/s vs 1.94±0.05×10-3mm^2/s). When measured 28 days later, the ADC of the effusions origin from chronic renal insufficiency showed an increasing pattern, but those of pneumonia and malignant effusions showed a decreasing pattern. The ADC values with b factor of 2000s/mm^2 are more comparable than the others because signal intensities of pleural fluids were more homogeneous.

Conclusions: ADC values may differentiate the character of different types of pleural effusion and both of the b factor and time factor affected the identification of pleural effusion.

Key words: Lung, pleural effusion, MR–magnetic resonance (MR), diffusion study.

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I. INTRODUCTION

Pleural effusion is a widespread clinical problem and it can arise from various diseases such as malignancy, heart failure, tuberculosis and other respiratory infections[1-3]. Pleural effusion is divided into transudate and exudate. The true diagnosis of the effusion is essential for patient management[4]. Because transudate effusions are mainly caused by systemic diseases. However, exudative effusions usually occur in local or systemic malignant tumors and inflammation. Almost all effusions of cancer are exudate[5]. It is important to distinguish between transudate and exudate. In the case that fluid is transudate, then the treatment process is carried out in underlying pathology without any further diagnostic procedures; however, if the effusion is an exudate, then this time a wide diagnostic investigation is needed[4]. It is necessary to perform pleural liquid analysis to recognize the pleural effusion origin, thereby ensuring the optimal treatment[6]. The pathological, biochemical as well as clinical performance shall be considered to perform diagnosis[7]. Biochemical analysis with regard to the liquid that is acquired from a thoracentesis effectively assist in differentiating transudate from exudate[7]. Although

thoracentesis is a routine method for evaluation of pleural effusion, it is aggressive and may cause some complications. The most common complication is pneumothorax thoracentesis[8]. Other common complications include cough, chest pain, the vasovagal reflux resulted from blood pressure reduction and bradycardia, pleural blank infection, hemothorax caused by hepatic or splenic lacerations, intercostal artery laceration, soft tissue infection, and tumor cell seeding due to needle tract[8]. Patients with fibrous thoracic or calcified pleura are unable to have a pleural puncture.

At present, the Light's criteria is used to diagnose the type of pleural effusion. The Light's criteria is based on the analysis of serum and pleural fluid lactate dehydrogenase and protein levels, which is the gold standard to distinguish transudate from exudate[9]. However, some studies have shown that the biochemical components of pleural effusion gradually increase in congestive heart failure patients after taking diuretics. For them, the Light's criteria can be misunderstood as exudate (29% of exudate). Repaired in serum pleura. The liquid protein gradient (>3.1 g/dL) is higher compared with the serum-pleural fluid albumin gradient (>1.2 g/dL). According to the Light's criteria, liver cirrhosis patients are misunderstood as exudate (18%), and the pleural effusion/serum albumin ratio (<0.6) demonstrated a higher diagnostic accuracy compared with protein or albumin gradient[9, 10]. Other

studies have shown that correct staining, culture, as well as pleural fluid cytology can also affect the assessment of local exudates[11].

In this case, non-invasive imaging methods can deal with the necessity of pleural biopsy as well as the relevant risks, such as conventional magnetic resonance imaging (MRI) based on the signal intensity of contrast agent and fat saturation in T1 and T2-weighted images fat T1 weighted image of degree and the measurement value of Hounsfield unit in the computed tomography (CT). Nevertheless, the imaging methods mentioned above have not achieved reliable results[12-15].

The researchers explored other methods that use other properties of water molecules to produce contrast after initially focusing on the relaxation characteristics of T1 and T2. Diffusion-weighted imaging (DWI) was jointly developed by researchers such as Stejskal, Tanner and Le Bihan[13]. The microstructure can be seen as the water molecule movement in tissue by DWI. This movement is called Brownian motion, caused by thermal agitation. When water molecules move within the organization's different restrictions and obstacles, the flow of water can cause the dispersion phase, this process will lose signal intensity. Then the ADC can be calculated to quantify the loss of signal intensity. The variation of the b value which mathematically relies on the diffusion encoding gradient waveforms can help to change imaging sequence sensitivity to the water

diffusion. In 1990s, Echo-Planar Imaging was available, which could contribute to the practical application DWI in the clinical imaging field[16, 17]. In the DWI sequence, diffusion sensitizing gradient refocusing pulse is applied to either side of 180°. The parameter "b value" determines the diffusion weight, in s/mm^2. It is proportionally associated with the square of the amplitude and the applied gradient duration. It is possible to qualitatively evaluate the diffusion on trace image and the quantitative evaluation is based on the parameter of apparent diffusion coefficient (ADC). Tissues which have restricted diffusion appear bright on the trace image and exhibit hyperintensity on the ADC map[18]. The diffusion sequence based on echo plane imaging is rapid and can deal with the motion artifacts.

Moseley et al.[19] together with Warach et al.[20] developed the DWI method for detecting acute stroke in early stage. With the application of echo plane imaging technology, the DWI sequence is applied to the chest, and this process will not cause image quality degradation due to motion artifacts.

As a non-invasive imaging method to replace thoracentesis, DWI can avoid the risks caused by unnecessary pleural biopsy. Some studies have shown that the diffusion gradient can be used to check pleural effusion[21, 22], but there are only a few research about pleural effusion with DWI. Therefore, the study aimed at evaluating the variation of the sequence of ADC values regarding the pleural effusion by virtue of the in vitro diffusion-weighted MR imaging.

II. Materials and methods

1. Patients and in vitro samples

We investigated 15 pleural effusions from patients between December 2011 and February 2012 in this study. 3 of them were female and 12 were male. The mean age was 62.3 years (range, 17-90 years). The causes of pleural effusions were infection (4 patients), trauma (4 patients), malignancy (4 patients) and chronic renal insufficiency (3 patients) (table 1).

The criteria for patient selection were as follow: (a) Pleural effusion can be obtained by pleural puncture (b) The cause of pleural effusion can be confirmed by clinical findings and pathology.

The patients were excluded from this study who cannot perform pleural puncture (patients with fibrous or calcified pleura), and the cause of pleural effusion is unclear. Otherwise, the radiologist deemed it inappropriate for other reasons.

Pleural effusions aspirated from 15 patients and divided the samples into four groups according to the causes of pleural effusions. All in vitro fluids were aspirated and kept in a 120 mL hermetically sealed container as research samples. In vitro

specimens of pleural fluid from patients were confirmed by review of clinical information, laboratory evaluation and pathology.

2. Imaging acquisition and MRI protocol

Single-shot echo-planar spin echo (EPI; echo planar imaging) DWI using 3 Tesla MRI scanner(Philips, Eindhoven, Netherlands) was performed with three b factors (500, 1000 and 2000 s/mm^2), TR/TE 7500ms/shortest, 6 channel torso coil, voxel size: RL/AP 2.5/2.5 mm, voxel slice 30, slice thickness 5mm. Fat shift direction is P. The ADC maps were generated automatically from the DW images obtained. Quantitative analyses were performed on a Brilliance Workstation (Philips, Eindhoven, Netherlands). The ADCs values of aspirated pleural fluids were measured on immediate day, 7, 14, and 28 days after aspiration at the ADCs map.

3. Statistical analysis

Statistical analyses were executed using SPSS version 25 software (SPSS, Chicago, IL, USA), the parameters were described using their mean and standard deviation. The mean ADC values of pleural effusions with 4 groups were at four time points compared using linear mixed model. P value<0.05 was considered statistically significant. The multiple comparisons were also used to define the

difference of ADC value of a particular group between different time points or to compare the significance of the ADC values of different groups at the same time. Multivariate Tests and Test of Within-Subjects Effects were supplement used to evaluate the diagnostic usefulness of DWI in differentiating exudate and transudate.

III. Results

Of the 15 pleural effusion, there were 4 infection, 4 trauma, 4 malignancy and 3 chronic renal insufficiency by clinical and laboratory information. Table 1 lists the causes of pleural effusions in the study group.

With b factors of 500, 1000 and 2000 s/mm^2, the initial ADCs of the traumatic effusions were significantly lower than the others. But there is not statistically significance in other three groups and between time sequence. When measuring 14 days later, the ADCs of the effusions of chronic renal insufficiency showed increasing pattern, but those of infectious and malignant effusions showed decreasing pattern. The ADCs values with b factors of 2000 s/mm^2 are more comparable than b factors of 500 and 1000 s/mm^2. The signal intensity of pleural fluids are more homogeneous with b factor of 2000 s/mm^2（Table 4）.

When b=2000 s/mm^2, group 1（infection）between the immediate day and the 7th day, the mean value of ADC tended to be stable. From the 7th day to the 28th day, the average value decreased from 1935.2mm^2/s to 1873.42mm^2/s. Group 2 (trauma) between the immediate day and the 14th day, have a sharp decreased from 1640 mm^2/s to 1305.5 mm^2/s and increased to 1386.9 mm^2/s rapidly on 14th

day. But it was always significantly lower than the other three groups from the immediate day to the 28th day, continually lower than 1640 mm^2/s. The third group (malignancy) had the highest ADC value on the immediate day than other 3 groups between the 14th day and from the 28th day, have a gentle decline. The group 4(chronic renal insufficiency) was similar to the third group on the immediate day, between the14th day and the 28th day, its ADC value increased rapidly to 1989.6 mm^2/s, which was significantly higher than other groups (Figure 1).

The ADC value is statistically different at different times, and the effect of the time factor varies with different groups (Table 2 and Table 3).

Table 1. Causes of pleural effusion.

Etiology	No of samples from patients
Infection	4
Trauma	4
Malignancy	4
Chronic renal insufficiency	3
Total	15

Table 2. The Test of Within-Subject Effects results of the evaluation for time factors and interaction between time and group for each b factor.

Test of Within-Subjects Effects

Measure: MEASURE_1

source		Type III Sum of Squares	df	Mean Square	F	Sig
time	Sphericity Assumed	38654.677	3	12884.892	10.266	.000
	Greenhouse-Geisser	38654.677	1.792	21570.286	10.266	.002
	Huynh-Feldt	38654.677	3.000	12884.892	10.266	.000
	Lower-bound	38654.677	1.000	38654.677	10.266	.013
time *group	Sphericity Assumed	113978.905	9	12664.323	10.090	.000
	Greenhouse-Geisser	113978.905	5.376	21201.036	10.090	.000
	Huynh-Feldt	113978.905	9.000	12664.323	10.090	.000
	Lower-bound	113978.905	3.000	37992.968	10.090	.004
Error(time* group)	Sphericity Assumed	30122.700	24	1255.113		
	Greenhouse-Geisser	30122.700	14.336	2101.153		
	Huynh-Feldt	30122.700	24.000	1255.113		
	Lower-bound	30122.700	8.000	3765.338		

The difference in ADC values at each time was statistically significant ($F=10.266$, $P=0.002<0.05$), and the interaction between time and each group was statistically significant ($F=10.09$, $P=0.000<0.05$).

Table 3. The Multivariate Test results of the complimentary evaluation for time factors and interaction between time and group for each b factor.

Multivariate Tests

Effect		Value	F	Hypothesis df	Error df	Sig
time	Pillai's Trace	.927	25.566b	3.000	6.000	.001
	Wilks' Lambda (λ)	.073	25.566b	3.000	6.000	.001
	Hotelling's Trace	12.783	25.566b	3.000	6.000	.001
	Roy's Largest Root	12.783	25.566b	3.000	6.000	.001
time*group	Pillai's Trace	1.940	4.882	9.000	24.000	.001
	Wilks' Lambda (λ)	.003	15.770	9.000	14.753	.000
	Hotelling's Trace	59.028	30.607	9.000	14.000	.000
	Roy's Largest Root	55.200	147.200c	3.000	8.000	.000

There are differences at various time ($P<0.05$) and there are differences in the interaction of time and group ($P<0.05$).

Table 4. Difference comparison of ADC value in the same group at different time and between different groups at the same time under the linear mixed mode and multiple comparison methods when b factor is 2000 s/mm^2.

b=2000 Result of LMM						
	Infection(G1) Estimated Mean(n=4)	Trauma(G2) Estimated Mean(n=4)	Malignancy(G3) Estimated Mean(n=4)	CRI(G4) Estimated Mean(n=3)	Time P-value	Overall P-value
시작일(T0)	1943.915	1735.250	1975.800	1980.933	0.277	Group: 0.029 Time: 0.001 Group*Time:0.002
7 일 후(T7)	1940.225	1434.775	1964.950	1946.700	0.008	
14 일 후(T14)	1890.225	1510.858	1984.075	1951.067	0.030	
28 일 후(T28)	1884.850	1562.125	1948.750	2042.933	0.023	
Group P-value	0.888	<0.001	0.891	0.183		

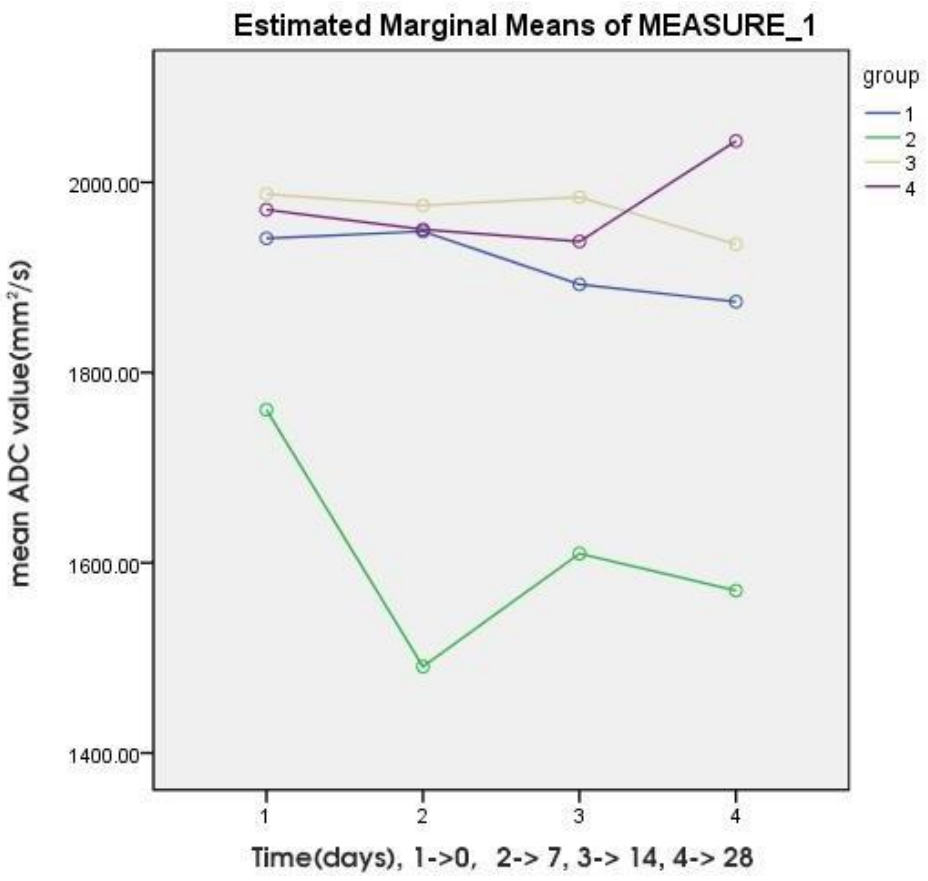
b=2000 P-value of Multiple Comparison (Time*Group)				
	시작일(T0)	7 일 후(T7)	14 일 후(T14)	28 일 후(T28)
G1 VS G2	0.176	0.004	0.016	0.018
G1 VS G3	0.831	0.979	0.799	0.723
G1 VS G4	0.626	0.968	0.872	0.586
G2 VS G3	0.123	0.004	0.01	0.009
G2 VS G4	0.093	0.006	0.018	0.009
G3 VS G4	0.768	0.949	0.94	0.826

b=2000 P-value of Multiple Comparison (Group*Time)				
	Infection(G1)	Trauma(G2)	Malignancy(G3)	CRI(G4)
T0 VS T7	0.881	<0.001	0.509	0.106
T0 VS T14	0.68	0.001	0.806	0.342
T0 VS T28	0.707	0.116	0.787	0.659
T7 VS T14	0.554	0.265	0.913	0.988
T7 VS T28	0.54	0.119	0.983	0.585
T14 VS T28	0.971	0.011	0.927	0.568

CRI: chronic renal insufficiency, G1: group1, G2: group2, G3: group3, G4: group4.

T0: immediate day, T7: 7 day, T14:14day, T28: 28day.

Figure 1. Profile plot of time and three group. B=2000s/mm^2, the trend of mean ADC value of 4 groups with 4 time.



When b=2000s/mm^2, the overall statistical results of linear mixed model showed significant differences in the mean value of ADC between each group(p-value<0.05) and between each time point(p-value<0.05), and significant interactions between time and group(p-value<0.05).

IV. DISCUSSION

The main findings of this study are as follows. First, ADC value was an imaging parameter characterized by noninvasiveness, reliability and reproducibility, which could assist in evaluating as well as characterizing pleural effusions. DWI is likely to help radiologist to characterize the pleural effusions. Second, when DWI was applied with the b values of 2000 s/mm^2, all the mean value of ADC in each group at 1, 7, 14, 28 day had statistical differences ($P<0.05$). The ADCs values with b factors of 2000s/mm^2, were more comparable than b factors 500 and1000 s/mm^2. Third, both of the time factor and b value of measuring pleural effusion had an effect on identification pleural fluid and prediction of the starting time of the disease with DWI. But except for the trauma group, the other groups did not provide sufficiently accurate time results. Further studies with regard to larger series shall confirm the results obtained from the present study.

Pleural effusions can be observed under various pathological conditions. Identifying pleural effusions as well as the related etiology is of vital significance[23]. The Light's criteria is applied as the first step in differentiating transudate from exudates[7]. The Light's criteria is the gold standard method for distinguishing

between transudates and exudates recently. Although the sensitivity of Light's criteria is sufficient, the specificity is relatively low, particularly in patients with congestive heart failure and transudates[18]. The protein content of pleural fluid increases as a result of diuresis in congestive heart failure treated with diuretics. Therefore, effusion may be misclassified as exudates[24]. In recent years, several studies have tried to identify various imaging techniques that can distinguish different types of pleural effusions (such as Ultrasound, CT and MRI). These techniques can be used to diagnose pleural effusions. Ultrasound, an existing radiological modality which is easy to use, can assist in detecting the localization and the septation of pleural effusions, as well as differing them from masses[25]. In spite of this, generally, pleural effusions cannot be sufficiently characterized through the calculation of CT attenuation values, the measurement of signal intensity in MRI and the application of contrasting contrast agents[12, 13]. DWI has become a novel approach to characterize pleural fluid at the molecular level[21].

DWI is a novel approach to characterize pleural fluid at the molecular level. In the literature, only three studies apply DWI for analyzing differentiated pleural fluid[26]. Compared with earlier studies[22], we used a single-shot spin-echoplanar imaging sequence that is not significantly affected by motion artifacts[27]. In earlier studies, the sequence may cause anatomical distortion due to its susceptibility

effect[28]. In a study involving 12 patients, Murtzet al.[28] adopted a single-shot spin-echoplanar imaging sequence which had electrocardiography triggering for minimizing the impact brought about by cardiac pulsations, finding that DWI performed without pulse triggering reduced the accuracy of the ADC calculation of the abdominal organs. Therefore, using the pulse trigger technology can help to improve the accuracy exhibited by ADC values in various fluids. In the present series, the study only focuses on the ADC value of the effusion and did not perform any quantitative and qualitative analysis on the DWI. In subsequent studies, DWI only changed one impact factors-b factors of 500 and 1000, ADC maps were qualitatively and quantitatively evaluated[29]. However, pulse-triggered DWI was not used in both studies which reduced the accuracy of measurements of ADCs[29-31]. In our study, not only ADC measurements were compared using 3-point techniques in the b-values of 0, 500, 1000 and 2000s/mm^2, patients' pleural fluid were divided into four groups according to different causes, but also another variable is the time of measuring ADC, we measured 4 times every sample for each b factor. In addition, all the original research directly affect the patient. Many patients would suffer respiratory distress, especially in the supine position[32]. To reduce the effects of breathing and cardiac motion artifacts and reduce distress, we used in vitro studies.

Our study has some advantages, for example, it is a totally non-invasive

method, and in this method, it does not require exposure to ionizing radiation. Moreover, after in vitro research and then to predict the time, reason, b-factors and ADC values can be distinguished, it can be directly applied to humans.

This study has several limitations. First, the sample size is small, and the number of subjects in the pleural effusion category is unevenly distributed. Further evaluation is necessary, including more patients with pleural effusion.

The Light criteria sensitivity is high enough, but has quite low specificity, especially for congestive heart failure patients[24]. Some literature have confirmed that among patients receiving diuretic therapy, 15%-30% of transudate may be misclassified as exudate by Light criteria[21].

Using 3T DWI, ADC values are detailed and analysis the cause of pleural fluid is performed simultaneously. ADC values can help us grasp the nature of pleural effusion. So far, the unexplored field-the image medical analysis of the human pleural fluid will find a new way. At present, there is no standard for ADC values. Because DWI is difficult to implement. But the originality of our institution makes the DWI protocol possible. Taking this opportunity, we hope to establish a comprehensive and absolute ADC values standard for beasts.

As the diagnosis of pleural fluid becomes easier, the treatment of patients' time is advanced. Also, even if you don't know about original cancer, you can find original cancer belatedly by conducting an MRI of pleural fluid.

Analyzing the time changes of the pleural fluid has never been tried. When the pleural fluid brings out is unknown. If the disease causes, disease classification, and time analysis in this study are carried out, a certain pattern of ADC values of pleural effusion can be identified. Then it can predict the starting time of the disease and the natural passage of pleural effusion in the future.

V. CONCLUSION

In summary, both b factors and time factors had statistical significance in distinguishing pleura effusion of different diseases. ADC value may be useful in evaluation and characterization of pleural effusions. The results from this study will provide a new direction to distinguish the pleural fluid by a non-invasive method.

Further study with a large number of samples is necessary to confirm our findings and further research with muti-b factors and accurate time should also be conducted on this topic.

List of abbreviations used

MRI: magnetic resonance imaging

DWI: Diffusion-weighted imaging

ADC: apparent diffusion coefficients

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ABSTRACT IN KOREAN(국문요약)

다중 파라미터 확산강조영상에서 각종의 질병 흉막삼출의 체외 스캔.

양홍뢰 (Honglei Yang)

연세대학교 대학원 의학과

<지도교수: 고성민>

목표: 체외 확산 가중 MR 영상촬영을 사용하여 흉막삼출물의 외관확산계수(ADC) 값의 순차적 변화를 평가하기 위함이다.

재료 및 방법: 흉막삼출 15 개 샘플(만성신부전 3 개, 감염 4 개, 악성 4 개, 외상 4 개)을 대상으로 하였다. 3 테슬라 자기공명영상을 이용한 싱글샷 에코-플래너 스핀 에코 DWI 는 3 개의 b 인자(500, 1000, 2000s/mm^2)를 사용하여 시행되었고 흉수 ADC 값은 1, 2, 4 주 후 ADCs 맵에서 측정되였다.

결과: 외상 흉막삼출의 ADC 는 다른 흉막삼출보다 매우 낮았다(1.62±1.25x10-3mm^2/s vs. 1.94±0.05x10-3mm^2/s). 28 일 후에 측정했을 때 만성 신부전증에서 비롯된 흉막삼출의 ADC 는 증가하는 패턴을 보였지만, 폐렴과 악성 흉막삼출은 감소하는 패턴을 보였다. B 인자 2000s/mm^2 의 ADC 값이 다른 b 인자의 ADC 값과는 통계적으로 유의한 차이를 보였다.

결론: ADC 값은 여러 유형의 흉막삼출의 특성을 평가할 수 있고 B 인자와 시간인자는 흉막삼출의 식별에 영향을 줄 수 있다.