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Differentiating Esophageal Small Cell Carcinoma from Esophageal Squamous Cell Carcinoma based on DWI, DKI, and IVIM: A prospective study

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Research Article

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Abstract

Background

Magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI), intravoxel incoherent motion imaging (IVIM), and diffusion kurtosis imaging (DKI), is a widely used approach for preoperative evaluation, pathological grading, and evaluation of the efficacy of chemoradiotherapy in patients with esophageal cancer. Yet, these methods have not been tested for differentiating esophageal small cell carcinoma (SCCE) from esophageal squamous cell carcinoma (ESCC).

Purpose

To evaluate the diagnostic value of IVIM, DKI, and DWI in distinguishing SCCE from ESCC.

Study type:

A prospective study.

Populations:

Fifty patients with esophageal carcinoma were selected (19 with SCCE and 31 with ESCC).

Sequence:

All subjects underwent sagittal IVIM, sagittal DWI, and sagittal DKI scans.

Assessment:

IVIM, DWI, and DKI parameters, including true diffusion coefficient (D), perfusion fraction (f), pseudo-diffusion coefficient (D^*), apparent diffusion coefficient (ADC), mean kurtosis (MK), and mean diffusivity (MD) were measured for each patient.

Statistical tests:

The bland-Altman method was used to analyze the repeatability and inducibility of imaging parameters; ANOVA test (normal distribution) or Kruskal-Wallis H test (non-normal distribution) was used to compare differences in parameters. ROC curve was used to analyze the diagnostic efficacy of each parameter in distinguishing esophageal SCCE from ESCC.

Results

Except for D*, ADC, D, and MD of ESCC were higher than those of esophageal SCCE, while f and MK were lower (all $P < 0.05$). The AUC of MK, MD, ADC, and D values was higher than that of the f value ($P < 0.05$), while the difference in the AUC values of MK, MD, ADC, and D was not statistically significant ($P > 0.05$).

Conclusion

IVIM and DKI can provide more information than DWI in differentiating SCCE from ESCC. MD, MK, D, and ADC feature a higher diagnostic efficacy.

Introduction

Esophageal cancer is the sixth most common cause of cancer-related death worldwide. It is highly present in East Asia, especially in northern and central China, where the incidence is maintained at more than one in one thousand all year round (1). Esophageal squamous cell carcinoma (ESCC) is the main histological subtype of esophageal cancer, accounting for more than 90% of all esophageal cancer cases. On the other hand, small cell carcinoma of the esophagus (SCCE) is a rare pathological subtype, which accounts for only about 0.4–2.8% of all esophageal malignancies (2, 3). It is a strongly invasive tumor, often leading to lymph node metastasis and poor prognosis (4, 5). Also, SCCE diagnosis is difficult.

Previous studies have suggested that MRI, especially diffusion sequences such as IVIM and DKI, may be useful for preoperative evaluation, pathological grading, and evaluation of the efficacy of chemoradiotherapy in patients with esophageal cancer (6–9). As a biexponential diffusion model, IVIM and DKI reflect the diffusion movement of water molecules in biological tissue cells under non-Gaussian distribution conditions and can identify microscopic characteristics of tumor cells (10, 11). However, there are no relevant studies on differentiating esophageal SCCE from ESCC using functional MRI.

The aim of this study was to examine the diagnostic value of IVIM, DKI, and DWI in distinguishing SCCE from ESCC.

Materials and methods

Patient data

From September 2019 to September 2021, 50 hospitalized patients (26 males and 24 females) with esophageal cancer admitted to the Shandong Provincial Hospital were selected. All patients received conventional MRI, sagittal DWI, sagittal DKI, and sagittal IVIM scanning. Inclusion criteria were: (1) patients with postoperative pathological confirmed ESCC or esophageal SCCE; (2) minimum diameter of imaging lesions ≥ 1 cm. Exclusion criteria were: (1) those who received preoperative chemoradiotherapy;

(2) image quality was poor (e.g., due to irregular breathing or other reasons); (3) with unclear pathological data.

Ethical approval and participation consent

This was a prospective study. All procedures were in accordance with the ethical standards of the institutional and national research councils, the 1964 Declaration of Helsinki, and its later amendments or similar ethical standards. Informed consent was obtained from all patients. This study was approved by the Clinical Research Ethics Committee of Shandong Provincial Hospital (Ethics Number SDPH325679).

Data acquisition

A 3.0T nuclear magnetic resonance scanner Simens 3.0T (Prisma, Germany) with an 18-channel phased array body coil was used. The patients were placed in a supine position. Prior to the examination, the patients received quiet breathing exercise training. The scan range should include the entire esophagus. The scanning sequences included sagittal T2WI sequence and coronal T2WI-HASTE, sagittal DWI, sagittal IVIM, and sagittal DKI (the above sequence scans were conducted in the free-breathing state) (**Table 1**).

Image analysis

Two radiologists (with more than 10 years of diagnostic experience) obtained IVIM and DKI original images S0 as a reference and delineated ROIs on ADC, D, D*, f, MD, and MK images (**Figure 1B-G** and **Figure 2B-G**). When delineating the ROIs, first, a whole lesion body was selected, avoiding cystic and necrotic areas; then, the level, location, size, and shape of the ROI on each image of ADC, D, D*, f, MD, and MK should be as close as possible. The mean value of ROI measurements at different levels was used as the final value. Each patient was measured three times at one-month intervals, and the average of the three measurements was finally used as the last value.

The original images of DWI, IVIM, and DKI of Body diffusion imaging 1.3.1 software of Simens post-processing workstation Syngo were used for processing. Calculation was conducted by using the DWI formula:

$Sb = S_0 \times exp\ (-b \times ADC),$

where Sb refers to the DWI signal intensity when the corresponding b value is applied and S_0 is the DWI signal intensity when no diffusion gradient field is applied. ADC values can quantitatively reflect a series of factors that limit the movement of water molecules, such as the density of tissue cells, the size of cell volume, and the amount of protein content in the extracellular space.

IVIM original image S0 processing was conducted by using the following calculation formula:

IVIM: S/So = f_{IVIM} exp [-b (D + D blood)] + (1-f_{IVIM}) exp (-b × D)*

where S/S0 is the sum of tissue and blood components, f_{IVIM} is the flowing blood fraction, D is the water diffusion coefficient in tissue, Dblood is the water diffusion coefficient in blood, and D^* represents the pseudo diffusion coefficient associated with microcirculatory perfusion factors, such as capillary structure in tissue. Among them, f_{IVIM} and D^* can effectively reflect microperfusion in tissues.

The following formula was used for the S0 image processing of DKI:

$$Sb=S0\times\exp(-b\times D+1/6b^2\times D^2\times K)$$

where K is diffusion kurtosis that can effectively reflect the deviation of water molecules from Gaussian motion and D is the apparent diffusion coefficient after correcting for non-Gaussian motion. This paper used MD to refer to D and MK to refer to K.

Pathological analysis

HE-stained sections were evaluated by two physicians (with more than 10 years of experience in pathological diagnosis) according to the WHO 2019 edition classification of gastrointestinal tumors. There were 31 cases of ESCC and 19 cases of SCCE of the esophagus.

Statistical analysis

Statistical software SPSS and Medcalc were used for data analysis. First, background information, such as patient height, weight, age, and gender ratio, as well as imaging parameters, were analyzed, and the corresponding values were expressed as mean value ± standard deviation. The repeatability and inducibility of each parameter between and within observers were studied using the Bland-Altman method. ANOVA test (normal distribution) or Kruskal-Wallis H test (non-normal distribution) was used to compare the background information, ADC, D, D*, f, MD, and MK parameters. ROC curve analysis was used to compare the diagnostic efficacy of DWI, IVIM, and DKI parameters in differentiating esophageal SCCE from esophageal squamous cell carcinoma. A p-value < 0.05 was considered to be statistically significant.

Results

A total of 50 esophageal cancer patients (19 with SCCE and 31 with ESCC) with complete pathological and imaging data were included in the study. ADC, D, D*, f, MD, and MK values were measured in each patient by two observers showing good consistency (**Table 2**).

The parametric images generated by sagittal DWI, IVIM, and DKI could effectively reflect the location and dynamic range of esophageal cancer (**Table 3**, **Figure 1A-G**, and **Figure 2A-G**). Of the 19 cases with esophageal SCCE, the tumor involved the middle and lower thoracic esophagus in 16 cases, while 3 cases had a tumor in the upper thoracic esophagus. Among 31 cases of ESCC, 24 involved the middle

and lower thoracic segments of the esophagus and 7 the upper thoracic and cervical segments of the esophagus.

As shown in **Table 4**, there was no significant difference in age, weight, height, and the male-to-female ratio between the two groups (all P > 0.05). There were 31 cases of esophageal poorly differentiated squamous cell carcinoma in group 1 and 19 cases of poorly differentiated esophageal SCCE in group 2. As shown in **Table 5**, except for D^*, there were significant differences in ADC, D, f, MD, and MK between the two groups (all P < 0.05). Compared with esophageal squamous cell carcinoma, esophageal SCCE had higher MK and f values and lower ADC, D, and MD values (all P < 0.05).

As shown in **Table 6**, the ROC curve was used to analyze the diagnostic efficacy of ADC, MD, MK, D, and f in distinguishing ESCC from esophageal SCCE (**Figure 3**). The diagnostic efficacy of MK was the highest, followed by MD, D value, and ADC value, while the AUC value of f was the lowest. The AUC of MK, MD, ADC, and D values were higher than that of the f value (P < 0.05), while the difference in AUC values of MK, MD, ADC, and D showed no significant difference (P > 0.05). However, the diagnostic sensitivity and specificity of MK, MD, and D were significantly higher than those of ADC (all P < 0.05).

Discussion

This study demonstrated that IVIM and DKI have good diagnostic efficacy in distinguishing ESCC from esophageal SCCE. DWI, IVIM, and DKI can effectively reflect the location of esophageal lesions (13, 14), which is of great value in determining the surgical plan (Fig. 1A-G, 2A-G). In this study, 16/19 SCCE cases were located in the esophagus' middle and lower thoracic segments. Among 31 ESCC cases, 24 were located in the middle and lower thoracic segments of the esophagus, 5 were in the upper esophagus, and 2 were located in the cervical segment of the esophagus; these data are consistent with the previous studies on esophageal SCCE and ESCC (15, 16).

In addition, we found that ADC, D, and MD values were lower, while MK and f values were higher in patients with esophageal SCCE compared to the ESCC group; there was no difference in the D* value between the two groups. Considering its low differentiation potential, esophageal SCCE is often accompanied by a tighter cell arrangement. In addition, a small cell volume and a higher nucleoplasmic ratio of esophageal SCCE led to a further reduction in the intracellular space compared to ESCC. Furthermore, the excessive proliferation of esophageal SCCE will lead to smaller intracellular and extracellular space, which affects the free diffusion of water molecules and ADC, MD, and D values. The results of this study are consistent with the previous findings on small-cell lung cancer and non-small-cell lung cancer (17–20). In addition, we found no significant difference in the AUC values of ADC, D, and MD. Compared with ADC, MD and D showed higher sensitivity and specificity in differentiating ESCC from esophageal SCCE. The possible reason is that the multi b-value IVIM model proposed by Le Bihan can eliminate the effect of microscopic perfusion through a series of combinations of low b-values and obtain D values reflecting the real diffusion while DKI was originally applied to study the central nervous system. Therefore, DKI can quantitatively analyze the diffusion deviation between intracellular and

extracellular water molecules and water molecules in the ideal state and can more accurately reflect the complexity of the microstructure of the tissue than DWI. At the same time, DKI can effectively inhibit the movement of unrelated molecules in the background using a series of ultra-high b values, thus producing MD values that more truly highlight the diffusion situation of water molecules in the region of interest (21–23).

In addition to the D* value, we also found that esophageal SCCE had higher MK and f values compared with ESCC. The main reason for the above differences between the two lies in the microstructure, such as microvascular perfusion. Several studies have shown that esophageal SCCE has a higher proliferation potential than esophageal squamous cell carcinoma, while there is no difference in necrosis and hemorrhage, which means that esophageal SCCE has a higher cell density, reducing the extracellular space. At the same time, the SCCE has a smaller cell size, less cytoplasm, and a higher nucleoplasmic ratio, which results in a smaller intracellular space (4, 24). However, the MK value in the DKI biexponential model represents the kurtosis of water molecule diffusion in tissue cells and is related to the tightness of tumor microcell structure. Smaller intracellular and extracellular spaces will further enhance the complexity of the microstructure, thus showing higher MK values. These results are also consistent with the conclusions about small cell lung cancer and non-small cell lung cancer (25–27).

The f value positively correlates with the microvessel density of tumor tissue. Some studies found that primary esophageal SCCE had a higher microvessel density than squamous cell carcinoma, which may explain the higher f value in esophageal SCCE (17, 28, 29). However, the AUC values of f were significantly lower than those of ADC, MD, D, and MK. The reason may be that excessive proliferation of esophageal SCCE is often accompanied by different degrees of necrosis, which affects the microvascular perfusion in the intercellular space to a certain extent, resulting in some heterogeneity between different individuals.

However, there was no significant difference in D* between esophageal SCCE and ESCC ($P > 0.05$). The possible reason may be that in addition to the heterogeneity of tumor tissue, there may be a more significant correlation between D* and the microvascular diameter of microscopic tissue. Still, there is no relevant literature demonstrating a difference in microvascular diameter between ESCC and esophageal SCCE. This may also be why there is no significant difference in D* between the two groups (29–31).

Conclusion

IVIM and DKI can provide more information than conventional DWI for differentiating esophageal SCCE from esophageal squamous cell carcinoma. MD, MK, D, and ADC feature higher diagnostic efficacy, while f features a lower diagnostic efficacy.

Declarations

Data availability statement

All data generated or analysed during this study are included in this published article.

Declaration of conflicting interests

The authors declare no competing financial interest. There is no conflict of interest or declaration by any author.

Ethics approval and consent to participate

This was a prospective study. All procedures were in accordance with the ethical standards of the institutional and national research councils, the 1964 Declaration of Helsinki, and its later amendments or similar ethical standards. Informed consent was obtained from all patients. This study was approved by the Clinical Research Ethics Committee of Shandong Provincial Hospital (Ethics Number SDPH325679).

Statements

The early version of this manuscript had been presented as an academic poster in the Graduate Program at the ESGAR 35th Annual Meeting and Postgraduate Course 2024 May 28-31.

The link is shown as follows:

https://esgar.org/fileadmin/media/ESGAR_2024/ESGAR24-FinalProgramme-WEB_read_only.pdf

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Tables

Tables are available in the Supplementary Files section.

Figures

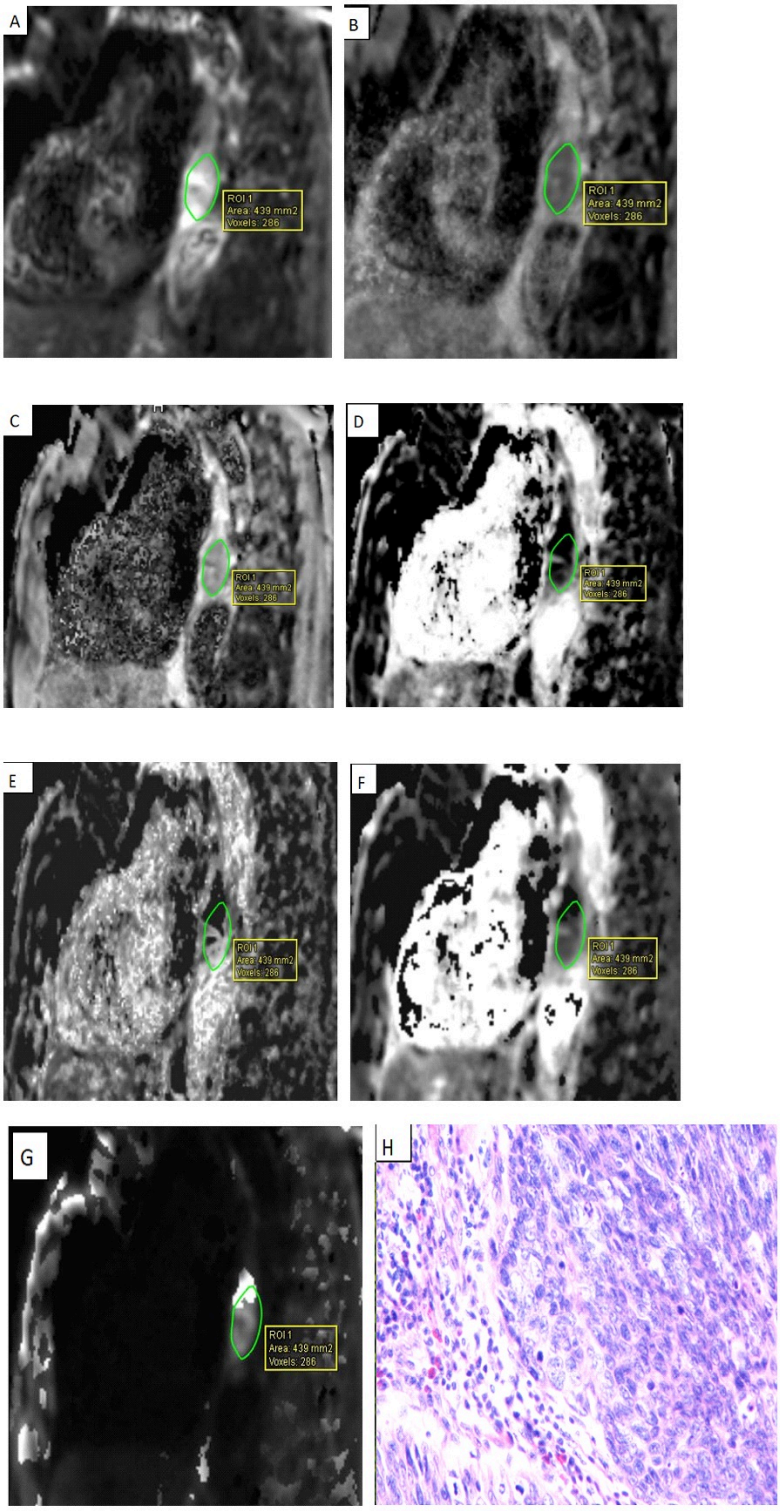


Figure 1

IVIM and DKI images and pathological image of esophageal squamous cell carcinoma in 56 years old patient (man). (A-G) A to G images represent S0, ADC, D, f, D^*, MD and MK images, respectively (D=1045mm^2/s, ADC=1128mm^2/s, D^*=247mm^2/s, f=383mm^2/s, MD=2593mm^2/s, MK=656 mm^2/s). **(H)** Microscopic pathological images showing a poorly differentiated esophageal squamous cell carcinoma (HE staining ×400).

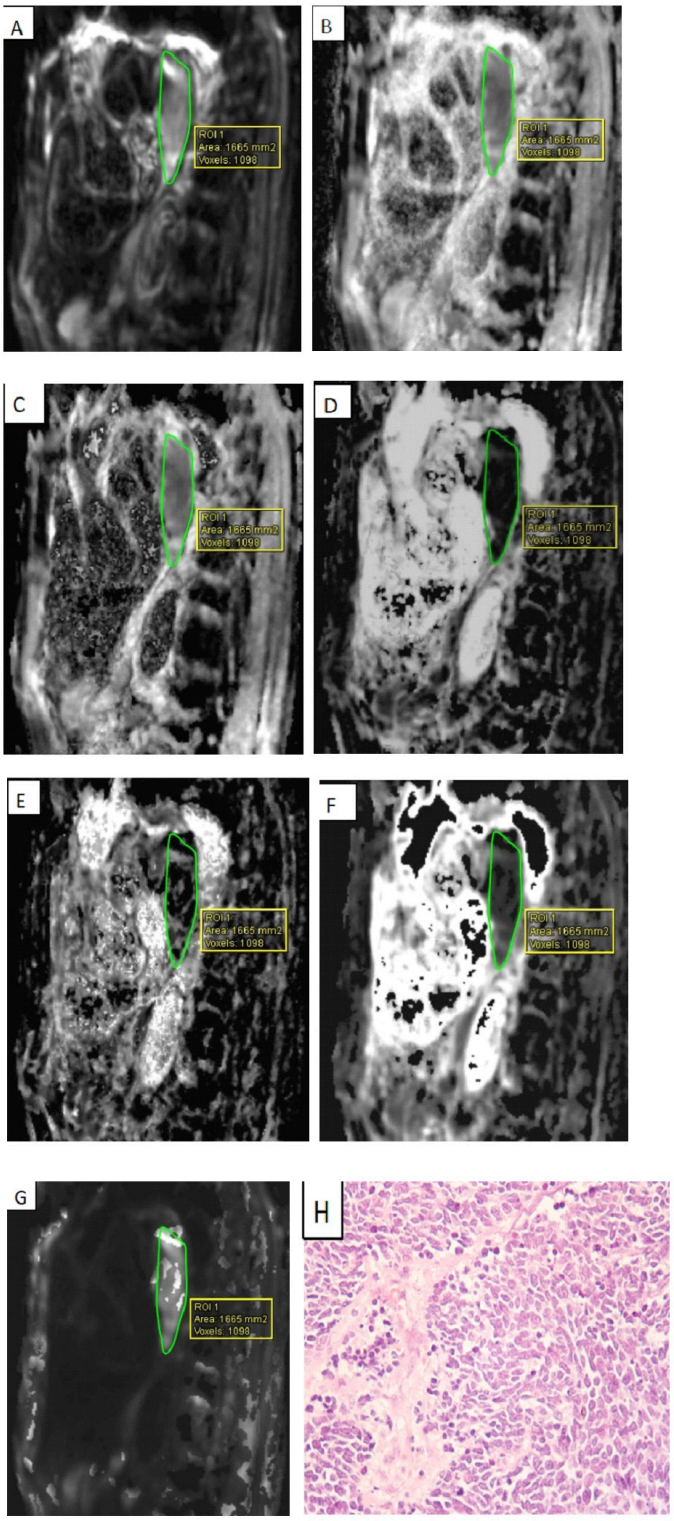


Figure 2

IVIM and DKI images and pathological image of esophageal small cell carcinoma in a 58 years old patient (male). (A-G) A to G images represent S0, ADC, D,f, D^*, MD, and MK images, respectively (D=935mm^2/s, ADC=952mm^2/s, D^*=251mm^2/s, f=515mm^2/s, MD=2310mm^2/s, MK=748mm^2/s). **(H)** Microscopic pathological images showing a poorly differentiated esophageal small cell carcinoma (HE staining ×400).

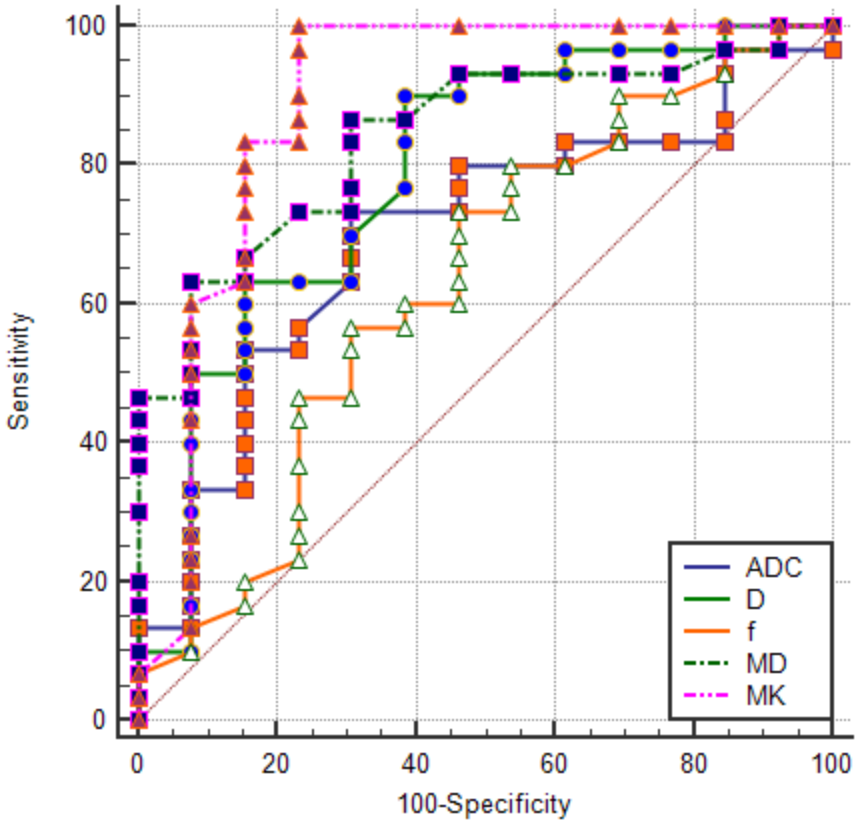


Figure 3

ROC curve analysis of MD, MK, D, f, and ADC. The AUC value of MK was the highest (AUC_{MK} = 0.896), and the AUC value of f was the lowest (AUC_f =0.632).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx