REVIEW ARTICLE

THE USE OF RADIOMIC ANALYSIS IN CARDIOVASCULAR DISEASES

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Abstract

A The recent years of the cardiovascular medicine saw a rapid development of advanced imaging modalities. The new era of personalized medicine takes advantage of what can be interpreted from medical images, searching for underlying connections between image phenotyping and biological characteristics to support precise clinical decisions. The application of radiomics in cardiovascular imaging has lagged behind other fields, such as oncology. While the current interpretation of cardiac and vascular images mainly depends on subjective and qualitative analysis, radiomics uses advanced image analysis to extract numerous quantitative features from digital images that are unrecognizable to the naked eye. The goal of this narrative review is to highlight the main findings of the recent use of radiomic analysis in the cardiovascular field. English-language articles published in the database PubMed were used for this review. The keywords used in the search included radiomics, cardiovascular or cardiac or aortic. Radiomics is expected to contribute to a more precise phenotyping of the cardiovascular disease, which can improve diagnostic, prognostic, and therapeutic decision making in the near future.

Keywords: *cardiovascular disease; aortic disease; radiomics.*

INTRODUCTION

The concept of radiomics was first described by Lambin and colleagues[1] in 2012. Radiomics assumes that images contain information specific of the disease that cannot be seen by human naked eye and, therefore, by extracting data regarding pixel distribution and interrelationship, extracts quantitative data.2 The main goal of radiomics is to extract quantitative features from images that can be used to guide clinical decisions, help in differential diagnosis, and predict treatment outcomes.[1, 3-5] Different types of medical imaging can be analyzed including magnetic resonance imaging (MRI), computed tomography (CT), positron-emission-tomography (PET)[2]. The workflow comprises image acquisition and segmentation (manual, automated or semi-automated) of the region of interest (ROI) (Figure 1). Next, features are extracted from this ROI with subsequent data analysis.[1, 2, 6]

Different types of radiomic features can be extracted from medical images. Using the software PyRadiomics (https://pyradiomics.readthedocs.io), these includes shape-based features, first-order statistic features, and texture-based features (Figure 2). Shape-based features are independent of gray level intensity and describe 2D- and 3D-geometric properties of the region of interest (ROI) like area, volume, perimeter, contours irregularity, and compactness (A). First-order statistic features describe the gray-level distribution within the ROI, without emphasis on spatial relationships (B). Texture-based features describe the spatial relationship between neighboring voxels

with different matrices (C).[2, 3, 6-10]

How to perform a radiomics analysis

A major challenge for the field of radiomics is the lack of reproducibility and validation of radiomic studies. The image biomarker standardization initiative1 aimed at standardizing the radiomics workflow from nomenclature to reporting guidelines and sets a general framework for radiomic analysis. All radiomic analysis follow these steps: 1) imaging and image processing; 2) radiomics features extraction; 3) feature selection and 4) data analysis.

1) Imaging and image processing

Radiomic analysis has been performed on CT[2], MRI[3] and PET[4] images. Depending on each vendor, different post-acquisition processing may be implemented on the final image (for example, suppressing artifacts created by metal objects). The extent of post-processing may limit the generalizability of the results if the analysis is to be repeated using images acquired on other vendors. These images are then segmented as to define the ROI in which radiomic features are extracted. This segmentation can either be made manually, for which there are several open-source softwares, such as 3D Slicer[5,6] and Horos[7]. Give the number of image studies required for a successful radiomics analysis (hundreds to thousands), manual segmentation emerges as a very time-consuming process and is subjected to intra- and inter observer variability. Semi-automated and fully automated algorithms were developed to aid on the segmentation of several anatomical structures, however they may lack external validity and the exported segmentation must be inspected manually.

2) Radiomic features extraction

After image acquisition and ROI segmentation, both products are read into an appropriate software for feature extraction. Several software may be used for radiomic feature extraction, namely open-source solutions such as Pyradiomics,[8] SlicerRadiomics (a radiomics extension for 3D Slicer that uses Pyradiomics library)[6,9] and Radiomics Image Analysis software package in the R environment.[10] Sometimes, investigators may use proprietary software. There may be some differences between software regarding feature extraction, so that must be kept in mind when extrapolating results to other software.

Several type of radiomic features can be extracted. Table 1 shows the most relevant family of features and their definition. The definitions follow the image biomarker standardization initiative.[1] As previously explained, these constitute quantitative translations of the voxels in the DICOM image.

3) Feature selection

Given the large number of radiomic features that may be extracted from each DICOM file (for example, Pyradiomics, on average, extracts ~1500 features per image) and that many of these features are correlated with each other (as they may represent transformations of one another), feature selection must be performed. Several algorithms for feature selection exist but they will not be outlined on this manuscript. Their objective is to reduce the number of input variables (i.e. radiomic features) to reduce the cost of modelling and to improve the model predictive performance.

4) Data analysis

Data analysis must be performed using adequate statistical methods to model the relationship between the radiomic features and the outcome of interest. This may be done through various methods, usually correlation (plots, logistic, linear, multiple). Usually, the study population is split into a development dataset (~80% of the population) and a testing or validation dataset (~20% of the patients). The performance of the model that was built on the previous steps may be assessed through receiver operating characteristic (ROC) curves parameters.[11]

CLINICAL APPLICATIONS

Coronary and cardiac diseases

The growing availability of dedicated cardiac CT for the assessment of coronary artery disease and the similar growing availability for cardiac MRI have allowed for the high throughput radiomic analysis of the generated images. Cardiac CT radiomic studies have mainly focused on two topics: epicardial adipose tissue and coronary plaques. It has been widely shown that adipocytes are not just quiescent cells, but they interact with neighboring structures via paracrine and vasocrine signaling. Radiomic analysis of perivascular adipose tissue has shown both correlations with the extent of adipose tissue inflammation and fibrosis[12] and with major adverse cardiovascular events including myocardial infarction.[12,13] Radiomic analysis of the epicardial adipose tissue also predicted the risk of post-operative atrial fibrillation in patients who underwent surgical aortic valve replacement.[14] Not all coronary plaques

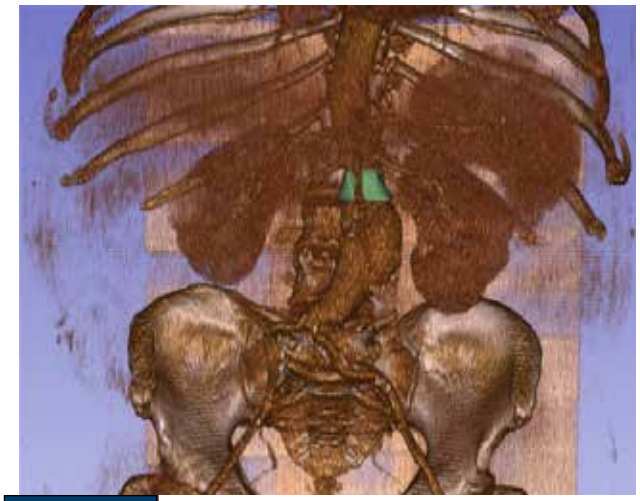

Figure 1 *Final aspect of the segmentation mask corresponding to the proximal neck of an abdominal aortic aneurysm in a 3D computed tomographic reconstruction.*

Table 1 **Families of radiomic features.**

Family	Definition
Morphological features	Describes geometric aspects of a ROI, such as area, volume and axis length.
Local intensity	Uses voxel intensities within a defined neighbourhood around a center voxel to compute local intensity features
Intensity-based statistics	Describes how intensities within the ROI are distributed.
Intensity histogram	Discretises the original intensity distribution into intensity bins.
Intensity-volume histogram	Describes the relationship between discretised intensity i and the fraction of the volume containing at least intensity i, ν27.
Grey level co-occurrence matrix	Expresses how combinations of discretised intensities (grey levels) of neighbouring pixels, or voxels in a 3D volume, are distributed along one of the image directions.
Grey level run length matrix	Assesses the distribution of discretised grey levels in an image, through assessing run lengths (defined as the length of a consecutive sequence of pixels or voxels with the same grey level along direction m).
Grey level size zone matrix	Counts the number of groups (or zones) of linked voxels. Voxels are linked if the neighbouring voxel has an identical discretised grey level. Whether a voxel classifies as a neighbour depends on its connectedness. In a 3D approach to texture analysis we consider 26-connectedness, which indicates that a center voxel is linked to all of the 26 neighbouring voxels with the same grey level.
Grey level distance zone matrix	Counts the number of groups (or zones) of linked voxels which share a specific discretised grey level value and possess the same distance to ROI edge. Captures the relation between location and grey level.
Neighbourhood grey tone difference matrix	Contains the sum of grey level differences of pixels/voxels with discretised grey level I and the average discretised grey level of neighbouring pixels/voxels within a Chebyshev distance δ.
Neighbouring grey level dependence matrix	Aims to capture the coarsness of the overall texture.

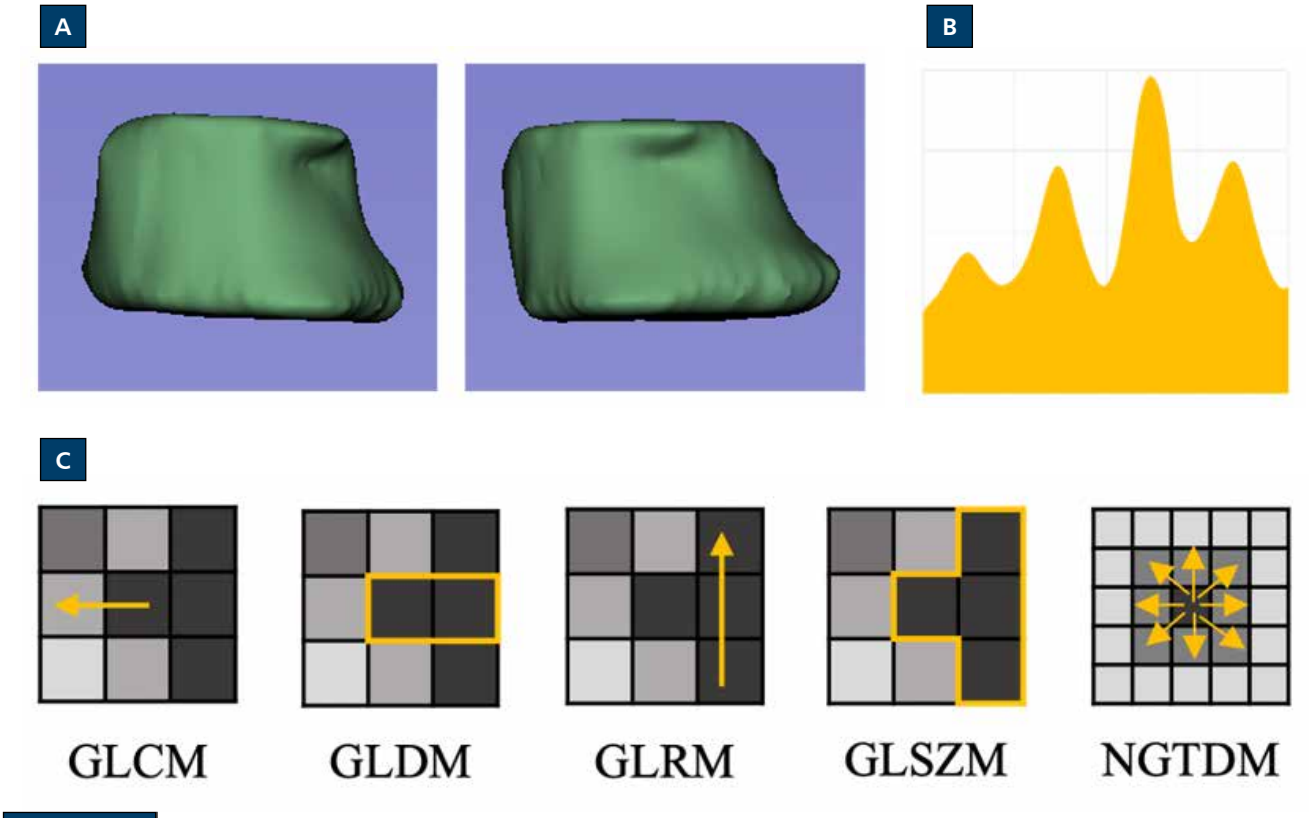

Figure 2

Radiomic features (adapted from 7, 9, 10). (A) Shape Features describe geometric features of the ROI. (B) First-Order Statistic Features are based on the gray level histogram and describe the distribution of the pixel intensities within the ROI without accounting their spatial relationships. (C) Texture-based Features reflect the spatial arrangement of pixels within the ROI, that is, it describe the relationship between neighboring pixels intensity with different matrices. These include GLCM that describe the relationship between pairs of pixels in a given direction and distance, GLDM that describes the gray level dependencies, that is defined as the number of voxels that have the same gray tone as the central voxel, GLRM that describe the number of runs of continuous pixels in one direction with same gray level intensity, GLSZM that describe the relationship between consecutive pixels with same gray level intensity, regardless of direction and NGTDM that describe the difference between the gray level of a pixel and its neighborhood. Legend: ROI, Region of Interest; GLCM, Gray Level Co-occurrence Matrix; GLRM, Gray Level Run-length Matrix; GLSZM, Gray Level Size Zone Matrix; NGTDM, Neighboring Gray Tone Difference Matrix; GLDM: Gray Level Dependence Matrix.

have the same risk of rupture. Vulnerable plaque detection may depend on a keen clinical eye and on other, more invasive, procedures. Radiomic analysis of coronary plaques has shown promising results on the detection of plaque vulnerability.[10,15,16] Single studies have also reported a role for cardiac CT radiomics on the further discrimination of clinically challenging situations. For example, one study reported the role of radiomic analysis to identify patients with left ventricular hypertrophy at a higher risk of heart failure or death.[17] Another study suggested a role of radiomics in distinguishing between the causes of prosthetic valve obstruction, namely pannus from other etiologies.[18]

Cardiac MRI studies have largely focused on patients with hypertrophic cardiomyopathy, given the prevalence of this disease and the need to better differentiate patient's prognosis, as to decide the type of therapy (i.e, implantable cardioverter-defibrillator implantation). Useful applications of radiomic analysis of cardiac MRI images in these patients may be related to the differentiation of the much more common hypertensive heart disease[19] and to detect the presence and extent of myocardial fibrosis.[11,20]

Despite promising, radiomics is still an investigational topic in cardiology and clinical application depends on further studies with the development of standardized tools for image acquisition and processing.

Aortic diseases

The value of the radiomic analysis has been demonstrated for both aortic aneurysms and dissections. Radiomic analysis predicted the aneurysm expansion after endovascular repair of abdominal aortic aneurysms (EVAR).[11] Early postoperative CT texture analysis was performed using three families of radiomic features—the grey-level co-occurrence matrix (GLCM), the grey-level run length matrix (GLRLM), and the grey-level difference method (GLDM). GLCM yielded the best performance (accuracy: 85%; AUC: 0.90), followed by GLRLM (accuracy: 87%; AUC: 0.86), and GLDM (accuracy: 86%; AUC: 0.83). All three texture features showed superi-

or predictive ability over clinical risk factors (accuracy: 69%; AUC: 0.66), conventional imaging features (accuracy: 69%; AUC: 0.67) and both combined (accuracy: 75%; AUC: 0.72). The ability to predict sac expansion after EVAR was also demonstrated in patients with type 2 endoleak after EVAR.[12] The radiomic features of the follow up CT scans (58 and 51 features from the one- and six-month CT scans, respectively) were used to develop a machine-learning model to predict the aneurysm sac dimension changes at one year. The classifier trained on one-month signatures was able to predict sac expansion at one year with an area under curve (AUC) of 89%, presenting 79% specificity and 100% sensitivity. Similarly, the classifier developed with six-month radiomics data showed an AUC of 96%, specificity of 91%, and sensitivity of 100%.

Guo et al.[13] and Zhou et al.[14] investigated the value of non-contrast CT-based radiomic signature in the diagnosis of acute aortic dissection. Radiomic features extracted from non-contrast CT images were used to widely and objectively screen for acute thoracic aortic syndromes. The predicted diagnosis was in good agreement with the probability of thoracic aortic dissections. The radiomic signature demonstrated AUCs, diagnostic accuracy, sensitivity, specificity of 90%, 90%, 86% and 92%, respectively, in one study[13] and 95%, 90%, 94% and 85%, respectively in the second study.[14]

Non-cardiovascular Diseases

Over the last years, radiomics have emerged as a method of analyzing medical images. The main goal of radiomics is to extract quantitative features from images that can be used to guide clinical decisions, help in differential diagnosis, and predict treatment outcomes.[1, 3-5] Radiomics has been applied in several medical areas such as molecular classification of tumors,[15, 16] tumor staging,[17] prognostic evaluation,[18, 19] and evaluation of diseases phenotypes such as coronary artery disease.[20, 21] This technology offers several advantages due to their non-invasive character, the possibility to account for intra-tumor heterogeneity by a complete analysis of the tumor, and inter-lesional heterogeneity analysis by sampling all the tumors within the same patient as well as the tumor microenvironment. [22]

LIMITATIONS

Cardiovascular radiomics has many challenges to overcome before it is feasible for daily clinical applications. The main limitations that impact its implementation in clinical practice include:[23-27] (a) its technical complexity; (b) need of standardization of the acquisition protocols and data analysis techniques to offer a robust framework; (c) improvement in reproducibility as it is affected by a series of factors including image acquisition, reconstruction, and analysis; (d) the manual segmentation of the target structures may cause higher interobserver variability and lower efficiency because the success of the procedure depends on the expertise of the operator; (e) the need for better accuracy in automatic segmentations.

CONCLUSION

Radiomic analysis can detect disease-specific and patient-specific information at a structural level that is not recognized to the naked eye, offering a deeper understanding of the link between imaging phenotyping and tissue pathology. This may have significant clinical implications and can contribute to clinical decision-making in cardiovascular diseases. Nevertheless, studies focusing on radiomics-based cardiovascular imaging need an overall improvement in the methodological quality. A more standardized methodology in the radiomics workflow is needed, especially in terms of study design and validation, in order to improve the feasibility of its clinical applications.

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