Avicenna.AI
empowering radiology with AI

CINA-VCF v1.0

User Guide

Caution: Federal law restricts this device to sale by or on the order of a physician.

AV-DP-CINA-VCF-10-013-SUM-USER-V02-EN-US
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Content

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OVERALL

1. Introduction

This user guide is intended to assist the User of CINA-VCF, developed, marketed, and owned by Avicenna.AI. It provides information for a better understanding and thus a better use of the CINA-VCF application.

2. Document overview

This document is composed of the main parts below:

- Intended use and indications for use
- Device description
- General caution and safety message
- CINA-VCF requirements for use
- Integration of CINA-VCF with 3rd party platform
- Cybersecurity and data protection
- Summary of the performance testing

3. Acronyms and Glossary

- Acronyms

VCF	Vertebral Compression Fracture
CT	Computed Tomography
DICOM	Digital Imaging and Communication in Medicine
HU	Hounsfield Unit
IAM	Identity and Access Management
MIP	Maximum Intensity projection
PACS	Picture Archiving and Communication System
ROC	Receiver Operator Characteristic
UDI	Unique Device Identification

- Glossary

Image Processing Application	The application reads the input file and generates the notification for incidental findings of vertebral compression fracture.
User	The CINA-VCF principal user. The end-users are trained medical specialists within standard-of-care bone health setting.

4. About this User's guide

The information contained herein is subject to change without notice. The only warranties for Avicenna.AI products and services are outlined in the express warranty statements accompanying such products and services. Nothing herein should be constructed as constituting an additional warranty. Avicenna.AI shall not be liable for technical or editorial errors or omissions contained herein.

- Screen captures

This guide uses screen captures to help illustrate various steps and procedures. The screen captures are used as examples only and may differ somewhat from what you see on your monitor.

- Feedback

Despite careful review, this manual may contain errors. Should further information be necessary or particular problems arise which are not covered sufficiently in this document, please contact us at support@avicenna.ai.

- Conventions

Caution messages indicate procedures which, if not observed, could result in possible problems with the device. Such problems include device malfunctions, device failure, damage to the device, or property damage. Do not proceed beyond a Caution message until the indicated conditions are fully understood and met.

Warning messages indicate procedures or practices that, if not observed, could result in potential harm to the patient or user (or environment). Do not proceed beyond a WARNING message until all of the indicated conditions are fully understood and met.

Notes are used to indicate information that may be helpful or of special interest to the reader.

Tips messages are used to give very useful information.

INTENDED USE AND INDICATIONS FOR USE

CINA-VCF is a radiological computer aided triage and notification software indicated for use in patients aged 50 years and over undergoing non-enhanced or contrast-enhanced CT scans which include the chest and/or abdomen.

The device is intended to assist hospital networks and appropriately trained medical specialists within the standard-of-care bone health setting in workflow triage by flagging and communication of suspected positive cases of Vertebral Compression Fractures (VCF) findings.

CINA-VCF uses an artificial intelligence algorithm to analyze images and highlight cases with detected findings on a standalone application in parallel to the ongoing standard of care image interpretation. The device does not alter the original medical image, and it is not intended to be used as a diagnostic device.

The results of CINA-VCF are intended to be used in conjunction with other patient information and based on professional judgment to assist with triage/prioritization of medical images. Notified clinicians are ultimately responsible for reviewing full images per the standard of care.

DEVICE DESCRIPTION

CINA-VCF is a radiological computer-assisted triage and notification software device.

CINA-VCF runs on a standard "off the shelf" server/workstation and consists of VCF Image Processing Application, which can be integrated, deployed and used with the CINA Platform (cleared under K200855) or other compatible medical image communications devices. CINA-VCF receives non-enhanced or contrast-enhanced CT scans (which include the chest and/or abdomen) identified by the CINA Platform or other compatible medical image communications device, processes them using algorithmic methods involving execution of multiple computational steps to identify suspected presence of Vertebral Compression Fractures (VCF) findings and generates results files to be transferred by CINA Platform or a similar medical image communications device for output to a PACS system or workstation for worklist prioritization.

DICOM images are received, recorded and filtered before processing. The series are processed chronologically by running algorithms on each series to detect suspected positive findings of a vertebral compressions fracture (VCF).

The device uses deep learning models to detect VCF at the T1-L5 level. The models were trained end-to-end on a dataset of 886 series collected from multiple centers in the USA and France satisfying the device protocol and representing a large distribution of scanner models from Siemens, Philips, GE and Canon (formerly Toshiba), acquisition protocols, spine presentation and fracture location and severity. Additional models, trained on subsets of this dataset, are used to locate the spine, identify the vertebra bodies and exclude vertebra which have been subjected to vertebroplasty or contains orthopedic material.

The Worklist Application displays all incoming suspect cases, each notified case is marked with an icon. In addition, compressed, grayscale, unannotated images that are captioned "not for diagnostic use" is displayed as a preview function. This compressed preview is meant for informational purposes only, does not contain any marking of the findings, and is not intended for diagnostic use beyond notification.

Presenting the specialist with worklist prioritization facilitates earlier triage by allowing prioritization of images in the PACS. Thus, the suspect case receives attention earlier than would have been the case in the standard of care practice alone.

The CINA Platform is an example of medical image communications platform for integrating and deploying the CINA-VCF image processing applications. It provides the necessary requirements for interoperability based on the standardized DICOM protocol and services to communicate with existing systems in the hospital radiology department such as CT modalities or other DICOM nodes (DICOM router or PACS for example). It is responsible for transferring, storing, converting formats, notifying of suspected findings and displaying medical device data such as radiological data. The CINA Platform server includes the Worklist client application which receives notifications from the CINA-VCF Image Processing application

GENERAL CAUTION AND SAFETY MESSAGES

• Potential Adverse Effects of Device on Health

There are no known direct safety or health risks caused by or related to the use of the CINA-VCF device. The device has no direct contact with the patient. Indirect risks are that the device may fail to flag and communicate suspected positive findings (false negative) of non-enhanced / contrast-enhanced CT scans (which include the chest and/or abdomen); or may flag and communicate some negative cases (false positive). Proper use of the information generated by the CINA-VCF device is explained in this manual. The CINA-VCF output is intended to be used in conjunction with other patient information and based on professional judgment to assist with the triage/prioritization of medical images.

• Intended patient population

CINA-VCF is intended to be used for adults aged 50 years and over undergoing non-enhanced / contrast-enhanced CT scans (which include the chest and/or abdomen).

• Limitations

CINA-VCF may fail to flag and communicate suspected positive findings of a vertebral compression fracture in the situations below:

- Significant motion artifacts
- Severe streak artifacts
- Notable image noise

Despite the data quality check performed by CINA-VCF on DICOM data (please refer to section: Image acquisition protocol requirements for optimal use), the aforementioned limitations refer to situations in which the device may fail to flag and communicate suspected positive findings (false negative) of vertebral compression fracture suspicion; or may flag and communicate some negative cases (false positive).

Warnings

Notifications include compressed preview images that are meant for informational purposes only and are neither intended for primary image interpretation nor diagnostic use beyond notification.

Cautions

Before use, please make sure that you have thoroughly read and fully understood all the caution and safety considerations outlined in this section.

To prevent incorrect use, the operator must know and apply the contents of the User Guide. Make sure that the correct version of the user guide is constantly at hand. Ensure periodic review of the procedures as well as the safety precautions.

The device is not intended to be used as a diagnostic device. The use of CINA-VCF can by no means replace a diagnosis by a licensed and competent physician nor constitute medical advice or diagnosis which can only be obtained from a physician. The physician bears the sole responsibility for the diagnosis.

The results of CINA-VCF are intended to be used in conjunction with other patient information and based on professional judgment to assist with the triage/prioritization of medical images. Notified clinicians are ultimately responsible for reviewing full images per the standard of care.

This medical software in no way replaces the competence and judgment of a qualified medical practitioner. It should only be used by qualified and trained personnel who are fully aware of the software's potential and limitations.

Avicenna.AI does not guarantee the quality, accuracy, or legality of images acquired with CT scanners based on which the software provides triage and notification. The user must, therefore, use caution when using the software.

CINA-VCF is compatible with the DICOM 3.0 standard, a format that allows the interchange of medical images. DICOM is a standard format for encoding and transmitting medical images. CINA-VCF is interoperable with CT scanners or PACS systems that meet this standard. The performance characteristics of CINA-VCF software have been assessed using the four main medical imaging equipment manufacturers (Canon Medical Systems Corporation, GE Healthcare, Philips Healthcare, and Siemens Healthineers).

Users must make sure that image series are complete and organized into properly ordered slices. For example, users should make sure the number of images in each series matches what is expected.

It is the User's responsibility to ensure that the input image datasets are complete and that no image or information is missing as results may not be reliable.

The modality operator is responsible for the input data's quality and the correctness of the patient information. Suboptimal data may induce suboptimal results.

CINA-VCF performs a quality check of the input data to make sure that each slice of the same DICOM series is consistent with the other ones (e.g., same series instance UID, modality, orientation, pixel spacing, slice thickness, number of rows and columns). Inconsistent DICOM series are rejected.

Effective use of CINA-VCF device requires adherence to CT imaging protocol requirements and the imaging manufacturer's instructions regarding the maintenance and calibration of the CT scanner.

Although CINA-VCF software is subjected to very thorough and intensive testing by Avicenna.AI, it is nevertheless possible unforeseen errors may arise during the use of this software. Users should at all times be aware and warned of such a possibility. Should the User notice dysfunctions or faulty behavior of the software liable to put the patient at risk, we strongly recommend that the user contact Avicenna.AI without delay at the following email address: support@avicenna.ai

CINA-VCF REQUIREMENTS FOR USE

1. Image acquisition protocol requirements for optimal use

The CINA-VCF image processing application is intended to be used on DICOM data that complies with the following acquisition protocol:

- Non-Enhanced or Contrast-enhanced CT scans which include the chest and/or abdomen:
  - DICOM CT Image Storage (1.2.840.10008.5.1.4.1.1.2) or Enhanced CT Image Storage (1.2.840.10008.5.1.4.1.1.2.1) SOP Class UID
  - DICOM Implicit VR Endian (1.2.840.10008.1.2), Explicit VR Little Endian (1.2.840.10008.1.2.1), Explicit VR Big Endian (1.2.840.10008.1.2.2), JPEG Lossless, Nonhierarchical, First-Order Prediction (1.2.840.10008.1.2.4.70) or JPEG 2000 Image Compression - Lossless Only (1.2.840.10008.1.2.4.90) Transfer Syntax UID
- Axial or sagittal acquisition
- Soft or standard tissue reconstruction kernel (*)
- Scans performed on adults ≥ 50 years of age
- Acquisition with homogeneous slice interval and without gap between successive slices
- Slice thickness ≤ 3 mm and ≤ 2 *slice interval to minimize MIP effects
- Slice interval ≤ 3 mm
- In plane resolution ≤ 1.25 mm * 1.25mm
- Field of view containing at least three consecutive measurable vertebrae in the T1-L5 portion of the spine without cement and surgical hardware.

CINA-VCF performs data quality check on DICOM data. If the DICOM data does not comply with the aforementioned protocol requirements, the image processing application will not be executed, and no result will be issued from the non-compliant data.

(*) CT scans acquired with a sharp reconstruction kernel will be rejected by the data quality check. CT scans acquired with a soft or standard reconstruction kernel will be accepted. The user will be informed in the preview image generated by the application if the reconstruction kernel is not identified with certainty by the application.

2. System requirements for optimal use

The CINA-VCF device has been designed to be used with the following minimal system configuration:

- CPU: 8 threads at 3.0+ GHz (supporting SSE4.2 and AVX2 instructions)
- Memory: 16 GB RAM

INTEGRATION OF CINA-VCF WITHIN 3RD PARTY PLATFORM

As with any other medical device software used in the radiology workflow, CT scans are made available to CINA-VCF through transmission functions. CINA-VCF can be integrated, deployed, and used with Medical Image Communications Devices (3rd-party Platforms).

The CINA-VCF device does not interface directly with any CT scanner or data collection equipment (e.g., PACS). This communication with the user's PACS or other user-specified radiology software system is ensured by the Medical Image Communications Device.

CINA-VCF receives non-enhanced / contrast-enhanced CT scans (which include the chest and/or abdomen) identified by a medical image communications device, processes them using algorithmic methods involving execution of multiple computational steps to identify suspected presence of VCF and generates results files to be transferred by a medical image communications device for output to a PACS system or workstation for worklist prioritization.

1. Resource requirements

The CINA-VCF image processing applications have been designed to be used with the following minimal system configuration:

- CPU: 8 threads at 3.0+ GHz (supporting SSE4.2 and AVX2 instructions)
- Memory: 16 GB RAM

2. Input data format

The CINA-VCF image processing applications take DICOM series provided by the 3rd party Platform in which they are integrated.

The platform is responsible for dispatching the relevant series to the CINA-VCF image processing applications. Avicenna.AI collaborates with the Platform's manufacturer to ensure that the Platform can efficiently fetch and dispatch patient data to CINA-VCF image processing applications.

3. CINA-VCF image processing application execution

CINA-VCF image processing application is instantiated by the Platform. It does not require any kind of user interaction. Depending on their integration within the 3rd party Platform, execution status or textual logs may be provided to the user. CINA-VCF image processing applications generate outputs and notifications which are made accessible to the user through the Platform. Please refer to the user guide from the manufacturer providing the system for additional information.

4. CINA-VCF image processing application outputs

- Notifications for cases with suspected VCF findings

CINA-VCF image processing application provides a case-level notification in case of suspected positive findings. This notification can be used by the 3rd party Platform to flag series in the Platform's Worklist (Figure 1) to assist trained specialists in workflow triage by flagging and communicating suspected positive findings of Vertebral Compression Fracture (VCF)

Figure 1 Illustrative example of a 3rd party Platform's Worklist with flagged series for cases with suspected VCF findings and Image processing application execution status

CINA-VCF image processing application also provides a textual description of the findings that can be used by the 3rd party Platform.

- **Vertebral compression fracture (VCF) application generated results**

The VCF image processing application analyzes Non-enhanced/Contrast-enhanced CT scans (which include the chest and/or abdomen) and flags and communicates suspected positive findings of Vertebral Compression Fractures (VCF).

The VCF image processing application is dependent on a series provided by the 3rd party Platform. It is the responsibility of the Platform to provide only suitable series to the application. In case of application execution on expected series or application execution on irrelevant series, please refer to the Platform's manufacturer user guide and support.

In case of positive findings of a vertebral compression fracture the image processing application provides the user with preview images where suspected positive findings of vertebral compression fracture have been detected.

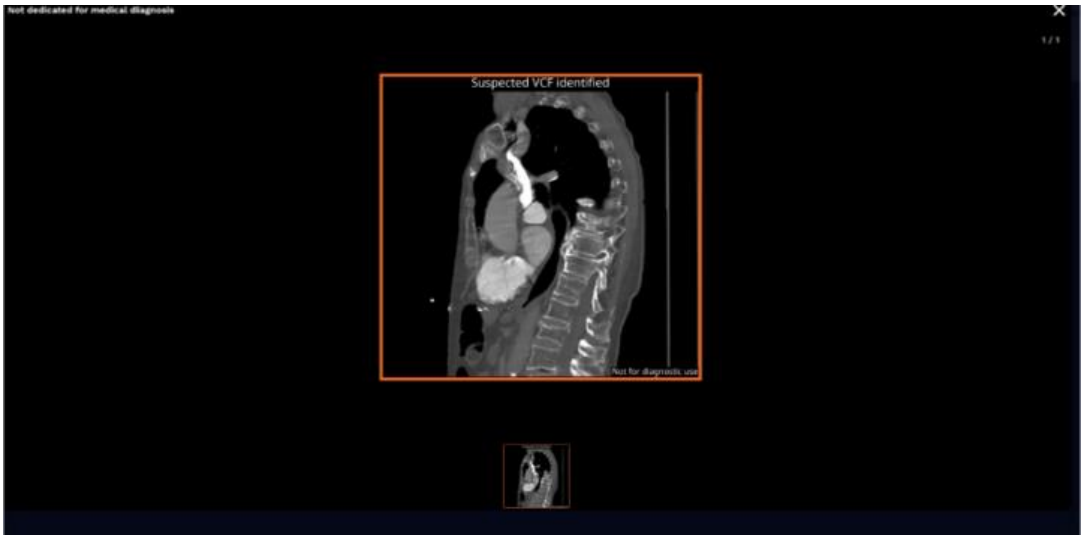
The preview image is provided in different formats:

- PNG
- DICOM Secondary Capture

It is intended to be used by the 3rd party Platform so that the user can verify the image-processing application results displayed on the Platform.

The DICOM SC and GSPS preview image contains the tag UDI Sequence Attribute (0018, 100A). The device UDI can be read in this dedicated DICOM tag. It allows for clear and unambiguous identification of Avicenna.AI devices on the market and facilitates their traceability.

In the illustrative example below (Figures 2a and 2b), a Platform user interface displays the preview image of the series where some findings of Vertebral Compression Fracture have been found. Figure 2c displays the case where a Vertebral Compression Fracture has not been identified.

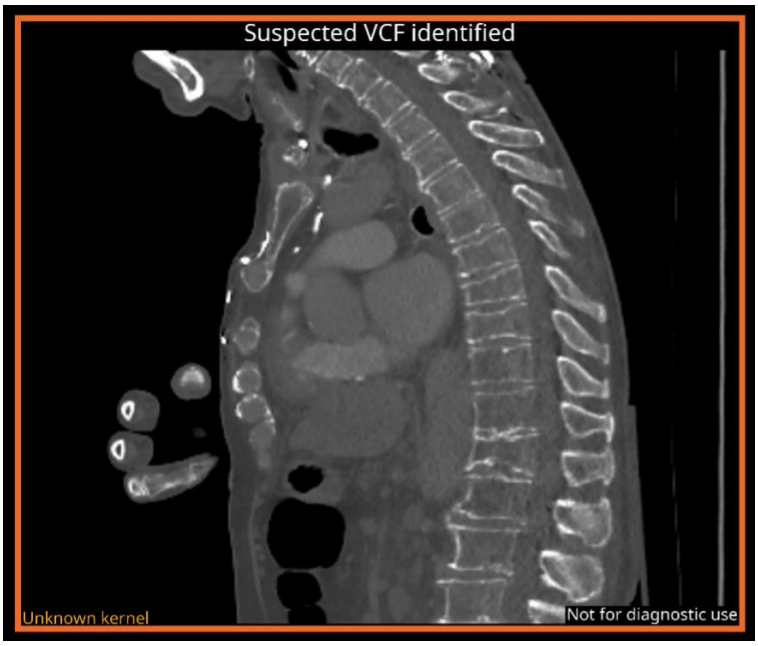

Not dedicated for medical diagnosis
Suspected VCF identified
Not for diagnostic use

Figures 2a, 2b and 2c Illustrative example of a 3rd party Platform user interface displaying results provided by the VCF image processing application

The viewer page contains one to three sagittal preview images depending on the number of vertebral compression fractures identified.

Preview images are framed with an orange contour in case a vertebral compression fracture has been identified. If not, the single preview image is framed with a blue contour.

In the illustrative example below (Figure 3), the CINA-VCF application is executed but the user is informed in the generated results that the reconstruction kernel is not identified with certainty by the application (i.e., “unknown kernel”).



Figures 3 Illustrative example of the message when the reconstruction kernel cannot be identified by the CINA-VCF application

Warning: Notifications may include one compressed preview image that is meant for informational purposes only, and is neither intended for primary image interpretation nor diagnostic use beyond notification.

CYBERSECURITY AND DATA PROTECTION

1. Login and password

CINA-VCF device is designed to manage and analyze data that contains sensitive patient information. Oblige to all HIPAA (Health Insurance Portability and Accountability Act) standards and local data protection laws in safeguarding all patient information and allow access to authorized users only.

CINA-VCF does not manage user identities and passwords for its functioning. However, users are reminded that usernames and passwords for the 3rd party platform that provides access to CINA-VCF results or files should not be shared with colleagues or others, even if they are permitted by law and site policy to view the same type of information. Users should be regularly trained on cybersecurity best practices.

It is also reminded that privileged and non-privileged users have access to a minimal set of Patient Health Information (PHI) and may not take snapshots, screenshots, or pictures (using another device) of any protected information viewed through the 3rd-party platform.

2. Storage and logs security

The CINA-VCF processing application is a stateless component that reads its inputs and produces its outputs into isolated folders using the volume mount feature of the container runtime. Such volumes must be configured with the least access rights privileges, read-only for the input folder receiving the CT images, write-only for the outputs, and owned by a technical or service account.

By design, the processing applications support a "fire and forget" execution model which can be leveraged to further reduce the window of data and application visibility.

After each application execution, a log file in JSON format is produced which contains the timings, identification of the processed series (without PHI information), and execution error codes if any. They can then be ingested by a HIPAA-compatible logging and auditing system.

The total storage needs for the temporary storage area are moderate as it acts as a temporary buffer. It could be initially sized according to an estimate of the number of scans multiplied by the average study storage volume expected to be on the waitlist, plus a reserve. However, the dynamic nature of the hospital workflows does require appropriate monitoring of the

storage capacity and recommends a solution providing dynamic or automatic capacity provisioning.

Finally, this storage area does not need backup or long-term storage as all the processing outputs will ultimately be pushed back to the PACS or re-created from the original DICOM data in the PACS if necessary. Moreover, depending on the applicable local policies concerning data recovery in case of hardware failure or ransomware attack, a simple reformat or creation of a new space is a possible option for a quick recovery if necessary.

3. Network and physical security

CINA-VCF should be integrated and used with medical image communications devices (3rd-party Platforms) and healthcare networks that take a global cybersecurity approach which includes risk management and policy development, proactive controls, and incident response. At a network level, this should include a cybersecurity approach to activities such as integration, media use, and asset management as well as secure network architecture with features such as strong authentication, anti-virus and anti-malware utilities, firewalls/gateways, and security event monitoring.

Authorized administrators should ensure that the CINA-VCF images have not been corrupted by comparing the image hash to the one provided by Avicenna.AI and that the container registry hosting the images is properly configured and secured.

CINA-VCF processing applications do not offer or require any networking service. This peculiarity can be leveraged at runtime by using an adequate configuration of the container runtime to remove any networking capability (i.e. with options like "–network none" or similar) as an extra security layer.

Administrators shall configure this solution according to the least access privilege rules in addition to the specific site rules to identify individuals requiring access to this application.

4. Reporting Security or privacy breaches

Users should inform their local IT department and the 3rd party Platform's manufacturer of any suspected or confirmed compromised user accounts and any other privacy or security breaches, including those that may provide access to CINA-VCF results or files. Please refer to the Platform's manufacturer user guide for recommendations about data protection and data security.

EXPECTED LIFETIME AND RATIONALE

Software is obsolete when the Operating System platform and hardware manufacturers stop the maintenance of the OS platform and/or hardware. Usually, OS platforms and hardware have an expected lifetime of three years.

In consequence, the lifetime of this product is three years from the date of version release/manufacturing date. Subsequent product releases may supersede this version or product before the lifetime limit.

LEGAL INFORMATION

- Copyright

- Avicenna.AI Trademarks

- Integrated 3rd-Party Software

Each integrated 3rd-party software is provided under Free and Open-Source Software (FOSS) licenses. For a detailed list please refer to the Platform's manufacturer.

COMPLAINTS AND INCIDENT REPORTING

Although CINA-VCF software is subjected to very thorough and intensive testing by Avicenna.AI, it is nevertheless possible unforeseen errors may arise during the use of this software. Users should at all times be aware and warned of such a possibility.
Should the User notice any dysfunctions or faulty behavior of the software, we recommend that the user contacts Avicenna.AI at the following email address: **support@avicenna.ai**

Any serious incident that has occurred with the CINA-VCF device should be reported to Avicenna.AI (using the email address: **support@avicenna.ai**) and the competent authority of the Member State in which the user and/or patient is established.

CONTACT

Manufacturer 	**AVICENNA.AI** Espace Mistral - Bâtiment A 297 Avenue du Mistral 13600 La Ciotat - FRANCE
Support and safety contact	Please contact the Platform's manufacturer for initial support. For additional assistance, please contact Avicenna.AI Customer Support. support@avicenna.ai
Website	https://avicenna.ai

APPENDIX I - SUMMARY OF THE PERFORMANCE TESTING

A retrospective, blinded, multicenter and multinational study with the CINA-VCF software was conducted with the primary endpoint to evaluate the software's performance in 474 non contrast-enhanced/contrast-enhanced Chest and/or Abdominal CT scans performed from another clinical indications than thoraco-lumbar vertebral compression fractures (VCF) evaluation. A secondary endpoint aimed to evaluate the time-to-notification (per-case processing time) effectiveness.

The data was provided from multiple clinical sources: 317 (66.9%) cases were US data and 157 (33.1%) OUS. There were 180 (37.9%) positive VCF (CT with VCF) included in the analyses.

EVALUATED DATA

The validation datasets contained sufficient numbers of cases from important cohorts in terms of clinical sources (e.g., US and OUS), imaging acquisitions (e.g., scanner makers, number of detector rows, kVp, slices thickness, acquisition views, acquisition protocols and reconstruction kernels), and patient groups (e.g., age, sex, and U.S. regions). Statistical distribution of cases among the categories was deemed to be suitable for the representativeness of the data used in the performance validation study. The validation dataset was separate from the ones used for the image processing application training and testing.

ANALYSIS

Two US board-certified expert radiologists proceeded to the visual assessment of the datasets to determine whether there is (or not) a suspected VCF on the CT images. In case of discrepancy between both radiologists, a third US board-certified radiologist reviewed the series, and the final ground truth was established by majority consensus. A case was considered positive if at least one moderate or severe vertebral compression fracture located within the thoracic or lumbar spine was identified by the experts.

All readers were blinded to each other. Visual assessments were performed separately. CT data were presented to each observer in separate reading sessions. None of the radiologists had access to CINA-VCF device results.

Separately, the same database was processed with the CINA-VCF device. The results were automatically computed and collected for further analysis. For each tested case, the time-to-notification (the time between receiving each DICOM case into the CINA platform and the positive/negative notification) was also recorded.

The comparison between the results provided by the US board-certified radiologists (the ground truth) and the ones automatically computed by the CINA-VCF device was performed according to the Area Under the Receiver Operating Characteristic (ROC) curves (AUC).

In addition, Sensitivity, Specificity and Accuracy were calculated, Finally, stratified statistical analyses on clinical sources (US and OUS), imaging acquisition parameters (scanner makers, number of detector rows, kVp, slice thickness, acquisition views, acquisition protocols and reconstruction kernels), and patient groups (age, sex, and US regions) were also calculated.

RESULTS

Among the 474 included cases, 166 (35.0%) were defined as positive and 308 (65.0%) as negative by the truthers. The identified confounding conditions by the truthers are listed in the table below:

Table 1: List and number of cases with defined confounding conditions.

Confounding Findings	Positive Cases	Negative Cases
Intervertebral disc vacuum phenomenon	93	106
Osteophytes	92	173
Schmorl's nodes	63	102
Scoliosis	11	13
Osteocondensation	9	34
Disc Space height Loss	42	93
Antherolisthesis/Retrolisthesis/Retropulsion	19	6
Ankylosing Spondylitis	10	8
Scheuermann	6	13
Sclerotic Lesion/Foci	7	10

Kyphosis	6	3
Motion Artifacts	1	4
Other Artifacts (i.e., streak and contrast media artifacts)	6	3
Noise	2	9
Vertebroplasty	7	2
Intervertebral Disc Calcifications	40	35
Hemangioma	5	5
Metastasis	0	1
Stenosis	2	1
Cupid bow	1	0
Demineralization	8	4
Lytic lesion	1	3
Osteonecrosis	4	0
Discitis osteomyelitis	0	1

Note that some cases presented more than one confounding finding.

- Primary endpoint:

CINA-VCF was able to demonstrate a ROC AUC of 0.974 [95% CI: 0.962 - 0.986], which exceeded the 0.95 performance goal, achieving its primary endpoint.

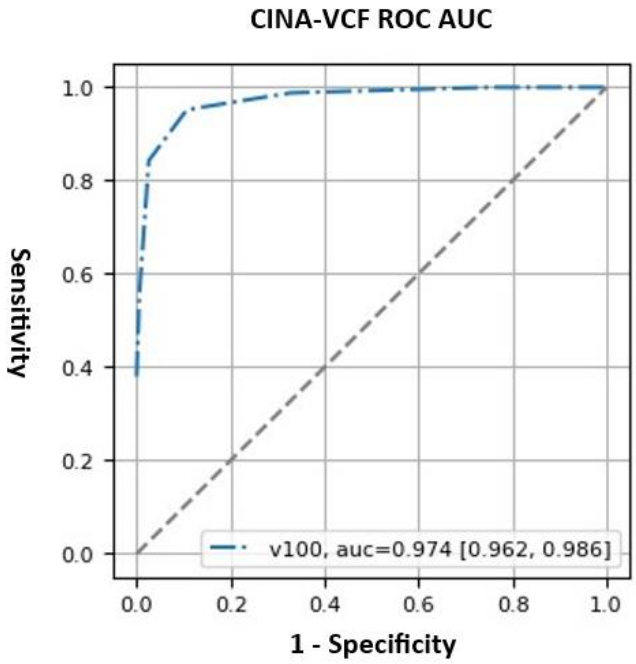


Figure 4. CINA-VCF area under the Receiver Operating curve.

- Additional Assessments:

Sensitivity and Specificity for the CINA-VCF prioritization and triage application were 95.2% [95% CI: 90.7% – 97.9%] and 92.9% [95% CI: 89.4% – 96.5%], respectively

In addition, the results of the current performance testing studies demonstrated an overall agreement (Accuracy) of 93.7% [95% CI: 91.1% - 95.7%] when compared to the ground truth (operators' visual assessments).

Positive predictive values (PPV) and negative predictive values (NPV), with varying prevalence, are provided in the table below:

Table 2: ALL DATA - Summary of Positive Predictive Values (PPV) and Negative Predictive Values (NPV) for CINA-VCF application, computed by varying prevalence values (from 5% to 50%, increments of 5

Prevalence (%)	PPV (%)	NPV (%)
5	41.4%	99.7%
10	59.7%	99.4%
15	70.2%	99.1%
20	76.9%	98.7%
25	81.6%	98.3%
30	85.1%	97.8%
35	87.8%	97.3%
40	89.9%	96.7%
45	91.6%	95.9%
50	93.0%	95.1%

Regarding US and OUS data, the results are summarized in the table below:

Table 3. US and OUS DATA: Summary of Positive Predictive Values (PPV) and Negative Predictive Values (NPV) for CINA-VCF application, computed by varying prevalence values (from 5% to 50%, increments of 5%).

Prevalence (%)	US DATA		OUS DATA	
	PPV (%)	NPV (%)	PPV (%)	NPV (%)
5	45.5%	99.9%	34.4%	99.4%

10	63.6%	99.8%	52.5%	98.7%
15	73.5%	99.7%	63.7%	98.0%
20	79.7%	99.5%	71.3%	97.2%
25	84.0%	99.4%	76.8%	96.3%
30	87.1%	99.2%	81.0%	95.3%
35	89.4%	99.0%	84.3%	94.1%
40	91.3%	98.7%	86.9%	92.8%
45	92.8%	98.4%	89.1%	91.4%
50	94.0%	98.1%	90.9%	89.6%

As presented in the tables above, overall NPV exceeded ranged between 95.1% for a prevalence of 50% and 99.7% for a prevalence of 5%. Overall PPV ranged between 41.4% for a prevalence of 5% and 93.0% for a prevalence of 50%. In fact, the PPV exceeded 80% for prevalence higher than 25%. For US and OUS data, the NPVs exceeded 89.6% whether for low or high prevalence and the PPV ranged from 34.4% to 94.0%.

Stratified analyses per sub-group cohorts are presented in the tables below.

a. Regarding the clinical sources (US and OUS):

Table 4: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding US and OUS data.

Clinical Sources	**Sensitivity (%) [95% CI] (TP ; FN)**	**Specificity (%) [95% CI] (TN ; FP)**
US (vRAD) (N = 317)	98.2% [93.5% - 99.8%] (TP = 107; FN = 2)	93.8% [89.5% - 96.6%] (TN = 195; FP = 13)
OUS (TeleDiag) (N = 157)	89.5% [78.5% - 96.0%] (TP = 51; FN = 6)	91.0% [83.6% - 95.8%] (TN = 91; FP = 9)

b. Regarding imaging acquisitions and scan parameters:

- Scanner makers

Table 5: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding the scanner makers.

Scanner makers	**Sensitivity (%) [95% CI] (TP ; FN)**	**Specificity (%) [95% CI] (TN ; FP)**
GE MEDICAL SYSTEMS (N = 168)	95.7% [89.2% - 98.8%] (TP = 88; FN = 4)	89.5% [80.3% - 95.3%] (TN = 68; FP = 8)
PHILIPS (N = 96)	96.4% [81.7% - 99.9%] (TP = 27; FN = 1)	98.5% [92.1% - 100.0%] (TN = 67; FP = 1)
SIEMENS (N = 130)	92.9% [76.5% - 99.1%] (TP = 26; FN = 2)	90.2% [82.7% - 95.2%] (TN = 92; FP = 10)
CANON (Formerly TOSHIBA) (N = 80)	94.4% [72.7% - 99.9%] (TP = 17; FN = 1)	95.2% [86.5% - 99.0%] (TN = 59; FP = 3)

- Number of detector rows

Table 6: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding the number of detector rows (NDR).

Number of detector rows (NDR) ranges	**Sensitivity (%) [95% CI] (TP ; FN)**	**Specificity (%) [95% CI] (TN ; FP)**
NDR < 64 (N = 116)	90.9% [70.8% - 98.9%] (TP = 20; FN = 2)	88.3% [80.0% - 94.0%] (TN = 83; FP = 11)
NDR ≥ 64 (N = 285)	94.8% [88.4% - 98.3%] (TP = 92; FN = 5)	94.7% [90.4% - 97.4%] (TN = 178; FP = 10)

- Slice Thickness

Table 7: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding the slice thickness (ST).

Slice thickness (ST) ranges	**Sensitivity (%) [95% CI] (TP ; FN)**	**Specificity (%) [95% CI] (TN ; FP)**
ST ≤ 1 mm (N = 90)	100.0% [82.4% - 100.0%] (TP = 19; FN = 0)	87.3% [77.3% - 94.0%] (TN = 62; FP = 9)
1 < ST < 3 mm (N = 242)	91.6% [84.1% - 96.3%] (TP = 87; FN = 8)	94.6% [89.6% - 97.6%] (TN = 139; FP = 8)
ST = 3 mm (N = 142)	100.0% [93.2% - 100.0%] (TP = 52; FN = 0)	94.4% [87.5% - 98.2%] (TN = 85; FP = 5)

- Peak Kilovoltage (kVp)

Table 8: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding the KVP.

Peak kilovoltage (kVp) ranges	**Sensitivity (%) [95% CI] (TP ; FN)**	**Specificity (%) [95% CI] (TN ; FP)**
80 < kVp < 120 (N = 76)	95.5% [77.2% - 99.9%] (TP = 21; FN = 1)	94.4% [84.6% - 98.8%] (TN = 51; FP = 3)
120 ≤ kVp ≤ 140 (N = 398)	95.1% [90.2% - 98.0%] (TP = 137; FN = 7)	92.5% [88.6% - 95.4%] (TN = 235; FP = 19)

- Acquisition view: Axial and Sagittal

Table 9: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding the CT acquisition view.

CT acquisition view	Sensitivity (%) [95% CI] (TP ; FN)	Specificity (%) [95% CI] (TN ; FP)
Axial (N = 236)	94.1% [85.6% - 98.4%] (TP = 64; FN = 4)	91.1% [85.7% - 94.9%] (TN = 153; FP = 15)
Sagittal (N = 238)	95.9% [89.9% - 98.9%] (TP = 94; FN = 4)	95.0% [90.0% - 98.0%] (TN = 133; FP = 7)

- Acquisition protocol 1: CT with or CT without contrast

Table 10: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding the CT acquisition: with and without contrast.

CT with and CT without contrast	Sensitivity (%) [95% CI] (TP ; FN)	Specificity (%) [95% CI] (TN ; FP)
CT with contrast (N = 259)	94.0% [86.7% - 98.0%] (TP = 79; FN = 5)	92.0% [86.9% - 95.6%] (TN = 161; FP = 14)
CT without contrast (N = 215)	96.3% [89.7% - 99.2%] (TP = 79; FN = 3)	94.0% [88.5% - 97.4%] (TN = 125; FP = 8)

- Acquisition protocol 2: Chest, Abdominal and Chest & Abdominal

Table 11: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding the CT acquisition: Chest, Abdominal or Chest & Abdominal.

Acquisition protocol 2: Chest, Abdominal and Chest & Abdominal	Sensitivity (%) [95% CI] (TP ; FN)	Specificity (%) [95% CI] (TN ; FP)

Chest (N = 169)	95.2% [86.7% - 99.0%] (TP = 60; FN = 3)	90.6% [83.3% - 95.4%] (TN = 96; FP = 10)
Abdominal (N = 194)	97.2% [90.3% - 99.7%] (TP = 70; FN = 2)	93.4% [87.5% - 97.1%] (TN = 114; FP = 8)
Chest & Abdominal (N = 111)	90.3% [74.2% - 98.0%] (TP = 28; FN = 3)	95.0% [87.7% - 98.6%] (TN = 76; FP = 4)

- Reconstruction Kernel

Table 12: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding the construction kernel.

Reconstruction Kernel	**Sensitivity (%) [95% CI] (TP ; FN)**	**Specificity (%) [95% CI] (TN ; FP)**
Soft tissues (Smooth) (N = 217)	95.0% [86.1% - 99.0%] (TP = 57; FN = 3)	92.4% [87.0% - 96.0%] (TN = 145; FP = 12)
Standard (N = 257)	95.3% [89.3% - 98.5%] (TP = 101; FN = 5)	93.4% [88.2% - 96.8%] (TN = 141; FP = 10)

c. Regarding patients' groups

- Patients' Ages

Table 13: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding Patients' Age.

Patients' ages ranges	**Sensitivity (%) [95% CI] (TP ; FN)**	**Specificity (%) [95% CI] (TN ; FP)**

50 ≤ Age ≤ 65 (N = 126)	94.1% [71.3% - 99.9%] (TP = 16; FN = 1)	95.4% [89.6% - 98.5%] (TN = 104; FP = 5)
65 < Age < 80 (N = 188)	98.3% [90.9% - 100.0%] (TP = 58; FN = 1)	92.2% [86.2% - 96.2%] (TN = 119; FP = 10)
Age ≥ 80 (N = 154)	93.3% [86.1% - 97.5%] (TP = 84; FN = 6)	89.1% [78.8% - 95.5%] (TN = 57; FP = 7)

- Patients' Sex

Table 14: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding Patients' Sex.

Patients' Sex	**Sensitivity (%) [95% CI] (TP ; FN)**	**Specificity (%) [95% CI] (TN ; FP)**
Male (N = 226)	96.7% [88.7% - 99.6%] (TP = 59; FN = 2)	90.9% [85.4% - 94.8%] (TN = 150; FP = 15)
Female (N = 241)	94.2% [87.8% - 97.8%] (TP = 97; FN = 6)	94.9% [89.8% - 97.9%] (TN = 131; FP = 7)

- Ethnicity - US Regions

Table 15: Stratified statistical analysis (Sensitivity, Specificity and 95%CI) regarding the US regions.

US regions	**Sensitivity (%) [95% CI] (TP ; FN)**	**Specificity (%) [95% CI] (TN ; FP)**
CONTINENTAL (N = 29)	100.0% [75.3% - 100.0%] (TP = 13; FN = 0)	100.0% [79.4% - 100.0%] (TN = 16; FP = 0)

NORTHEAST (N = 185)	96.6% [88.3% - 99.6%] (TP = 57; FN = 2)	90.5% [84.0% - 95.0%] (TN = 114; FP = 12)
PACIFIC (N = 23)	100.0% [78.2% - 100.0%] (TP = 15; FN = 0)	100.0% [63.1% - 100.0%] (TN = 8; FP = 0)
SOUTHEAST (N = 79)	100.0% [84.6% - 100.0%] (TP = 22; FN = 0)	98.2% [90.6% - 100.0%] (TN = 56; FP = 1)

The stratified statistical analysis (**Tables 4** to **15**) showed that all the sensitivities ranged between 89.5% and 100%. Regarding the specificities, values ranged between 87.3% and 100%. Indeed, all stratified subgroups obtained both sensitivities and specificities higher than 80%, which indicates a high performance.

The standalone performance testing demonstrated that the proposed device provides an accurate representation of key processing parameters under a range of clinically relevant parameters. It also demonstrated the generalized performance for a range of typical patient demographics (age, sex, and US regions) and a typical range of cases (scanner makers, number of detector rows, kVp, and slice thickness, acquisition views, acquisition protocols and reconstruction kernels).

- Secondary endpoint:

Per-case processing time (time-to-notification) of CINA-VCF image processing applications are presented in the table below:

Table 16: Time-to-notification statistics for CINA-VCF application.

Time-to-Notification (seconds)	MEAN ± SD	MEDIAN	95% CI	MIN	MAX
CINA-VCF All cases (N = 474)	23.4 ± 8.4	21.0	[22.7 - 24.2]	9.0	60.0
CINA-VCF True Positive cases (N = 158)	21.7 ± 7.5	20.0	[20.5 - 22.8]	9.0	45.0

APPENDIX II – ALGORITHM OVERVIEW AND DATASETS STRATIFICATION

CINA-VCF uses an artificial intelligence algorithm to analyze images and highlight cases with detected moderate or severe vertebra compression fractures at the T1-L5 level on a standalone application in parallel to the ongoing standard of care image interpretation. The user is presented with notifications for cases with suspected VCF findings.

The model has been trained end-to-end on a dataset of 886 series collected from multiple centers in the USA and France satisfying the device protocol and representing a large distribution of scanner models from Siemens, Philips, GE and Canon (formerly Toshiba) and acquisition protocols. Key demographic and clinical conditions are summarized in the tables below:

Table 17: By sources

Source Type	Cases (N=886)
Europe	50.8% (N=450)
USA	49.2% (N=436)

Table 18: By Manufacturer

Manufacturer	Cases (N=886)
Canon Medical Systems	25.7% (N=228)
GE Medical Systems	27.7% (N=245)

Philips	20.8% (N=184)
Siemens	25.7% (N=228)
Other	0.1% (N=1)

Table 19: By orientation

Orientation	Cases (N=886)
Axial (native)	85.1% (N=754)
Sagittal (reformat)	14.9% (N=132)

Table 20: By presence of contrast agent

Contrast Type	Cases (N=886)
Without contrast	35.2% (N=312)
With contrast	64.8% (N=574)

Table 21: By slice thickness

Slice Interval	Cases (N=886)
<=1.25mm	85.3% (N=756)
>1.25mm and <=3mm	14.7% (N=130)

Table 22: By patient age

Age	Cases (N=886)
50 to 60	22.0% (N=195)
60 to 70	27.9% (N=247)
70 to 80	40.3% (N=357)
80 to 90	7.9% (N=70)
90 and older	1.9% (N=17)

Table 23: By patient gender

Gender	Cases (N=886)
Male	53.4% (N=473)
Female	46.6% (N=413)

Table 24: By vertebra level

Vertebra	Percentage (N)	Vertebra	Percentage (N)	Vertebra	Percentage (N)
T1	4.40% (N=499)	T7	6.41% (N=727)	L1	7.34% (N=833)
T2	4.38% (N=497)	T8	7.21% (N=818)	L2	6.33% (N=718)
T3	4.40% (N=499)	T9	7.60% (N=863)	L3	5.25% (N=596)

T4	4.41% (N=501)	T10	7.73% (N=877)	L4	4.59% (N=521)
T5	4.67% (N=530)	T11	7.75% (N=879)	L5	4.40% (N=499)
T6	5.45% (N=619)	T12	7.68% (N=872)		

Of note, this dataset contains a representation of the most common confounding factors:

Table 25: List of defined confounding conditions.

Confounding factor
Inter-vertebral disc vacuum phenomenon
Osteophytes
Schmorl's nodes
Scoliosis
Osteocondensation
Disc Space Height Loss
Antherolisthesis/Retrolisthesis/Retropulsion
Ankylosing Spondylitis
Sclerotic Lesion/Foci
Vertebroplasty
Intervertebral Disc Calcifications
Hemangioma
Metastasis
Vertebral/Disc hardware

Additional models, trained on subsets of this dataset, are used to locate the spine, identify the vertebra bodies and exclude vertebrae which have been subjected to vertebroplasty or may contain orthopedic material.

The case level triage condition is based on comparing the maximum height loss computed by the algorithm on the candidate vertebrae, with an internal threshold defined through a sensitivity analysis performed on an external and independent dataset.