SIEMENS

ADVIA Centaur®
Immunoassay Systems

Interleukin-6 (IL6)

For Use Under Emergency Use Authorization (EUA) Only
For *in vitro* diagnostic use.
For prescription use only.

Current Revision and Date[a]	Rev. D, 2020-12		
Product Name	ADVIA Centaur IL6 assay	REF	10995080
Systems	ADVIA Centaur XP system ADVIA Centaur XPT system ADVIA Centaur CP system		
Materials Required but Not Provided	ADVIA Centaur Ancillary Probe Wash 3[b]	REF	10699211
	ADVIA Centaur Wash 1 (2 x 1500 mL)	REF	01137199
	ADVIA Centaur Wash 1 (2 x 2500 mL)	REF	03773025
Optional Materials	ADVIA Centaur IL6 Quality Control	REF	10995083
	ADVIA Centaur Multi-Diluent 13	REF	10492364
Specimen Types	Serum, plasma (potassium EDTA, lithium heparin)		
Measuring Interval	3.0–5500.0 pg/mL		
Reagent Storage	2–8° C		
Reagent On-System Stability	28 days		

[a] In Rev. B or later, a vertical bar in the margin indicates a technical update to the previous version.
[b] Needed for the ADVIA Centaur CP system only.

Warnings and Precautions

For Use Under Emergency Use Authorization

Only. For *in vitro* diagnostic use. For prescription

use only.

This test has not been FDA cleared or approved; the test has been authorized by FDA under an Emergency Use Authorization (EUA) for use by laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. 263a, to perform moderate or high-complexity tests.

This test has been authorized only for the quantitative measurement of IL-6.

This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of *in vitro* diagnostic tests for measurement of IL-6 under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C.

§ 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Federal (USA) law restricts this device to sale by or on the order of a licensed

healthcare professional.

Intended Use

The ADVIA Centaur® Interleukin-6 (IL6) assay is for *in vitro* diagnostic use in the quantitative measurement of interleukin-6 (IL-6) in human serum or plasma (potassium EDTA and lithium heparin) using the ADVIA Centaur® XP, ADVIA Centaur XPT, and ADVIA Centaur CP systems. This assay is used to assist in identifying severe inflammatory response in patients with confirmed COVID-19 illness to aid in determining the risk of intubation with mechanical ventilation, in conjunction with clinical findings and the results of other laboratory testing.

The ADVIA Centaur Interleukin-6 assay is a chemiluminescent immunoassay.

Normal IL-6 results do not preclude development of a severe inflammatory response, and IL-6 should not be used as the sole basis for patient management decisions. Results must be combined with clinical observations, patient history, other laboratory parameters, and epidemiological information.

The ADVIA Centaur® IL6 assay is only for use under the Food and Drug Administration's Emergency Use Authorization. For use by health care providers. For prescription use only. For *in vitro* diagnostic use only.

Testing is limited to laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform moderate or high complexity tests.

Test Principle

The ADVIA Centaur IL6 assay is a fully automated, one-step direct immunoassay using chemiluminescent technology, performed on the ADVIA Centaur XP, ADVIA Centaur XPT, and ADVIA Centaur CP systems. The assay utilizes an acridinium ester-labeled monoclonal mouse anti-IL-6 antibody as the Lite Reagent. The Solid Phase consists of anti-IL-6 mouse monoclonal antibody coated paramagnetic microparticles. The sample is incubated with the Lite Reagent and Solid Phase reagent to allow formed immune complexes to be captured by the particles. After incubation, the particles are washed before addition of the ADVIA Centaur Acid Reagent and ADVIA Centaur Base Reagent to initiate the chemiluminescent reaction.

A direct relationship exists between the amount of IL-6 present in the patient sample and the amount of RLUs detected by the system.

Reagents

Reagent	Description	Storage	Reagent Stability
ADVIA Centaur IL6 ReadyPack® primary reagent pack; Lite Reagent	10.0 mL/reagent pack monoclonal mouse anti-IL-6 antibody (0.5 µg/mL) labeled with acridinium ester in buffer with bovine serum albumin, surfactants, sodium azide (< 0.1%), and preservatives	2–8° C	**Unopened:** Stable until the expiration date on product **On-system:** 28 days
ADVIA Centaur IL6 ReadyPack primary reagent pack; Solid Phase	14.0 mL/reagent pack monoclonal mouse anti-IL-6 antibody coated paramagnetic microparticles (0.1 mg/mL) in buffer with bovine serum albumin, surfactant, and preservative	2–8° C	**Unopened:** Stable until the expiration date on product **On-system:** 28 days
ADVIA Centaur IL6 Calibrator	2.0 mL/vial after reconstitution, recombinant human IL-6, bovine serum albumin, and preservatives	2–8° C	**Unopened:** (Lyophilized) Stable until the expiration date on product
		2–8° C	**Reconstituted:** 30 days

On-system: 8 hours

Reagent	Description	Storage	Reagent Stability
ADVIA Centaur Interleukin-6 Quality Control[a]	7.0 mL/vial; lyophilized After reconstitution, three levels of recombinant human IL-6; bovine serum albumin; preservatives	2–8° C	**Unopened:** (Lyophilized) Stable until the expiration date on product **Reconstituted:** 30 days **On-system:** 8 hours
ADVIA Centaur ancillary reagent pack; Ancillary Probe Wash 3[b]	25.0 mL/reagent pack phosphate-buffered saline, sodium azide (< 0.1%), and surfactant	2–8° C	**Unopened:** Stable until the expiration date on product **On-system:** 28 consecutive days after the ancillary reagent pack is pierced
ADVIA Centaur ReadyPack ancillary reagent pack; Multi-Diluent 13[a]	10 mL/pack buffer with surfactant and sodium azide (< 0.1%)	2–8° C	**Unopened:** Stable until the expiration date on product **On-system:** 28 consecutive days after the pack is pierced
ADVIA Centaur Wash 1[b]	1500 mL/pack phosphate-buffered saline with sodium azide (< 0.1%) and surfactant	2–25° C	**Unopened:** Stable until the expiration date on product **On-system:** 1 month
ADVIA Centaur Wash 1[b]	2500 mL/pack phosphate-buffered saline with sodium azide (< 0.1%) and surfactant	2–25° C	**Unopened:** Stable until the expiration date on product **On-system:** 1 month

[a] Refer to *Optional Materials.*

[b] Refer to *Materials Required but Not Provided.*

Safety data sheets (MSDS/SDS) are available on siemens-healthineers.com.

H317
P261, P272, P280, P302 + P352, P333 + P313, P363, P501

Warning!
May cause an allergic skin reaction.
Avoid breathing dust. Contaminated work clothing should not be allowed out of the workplace. Wear protective gloves/protective clothing/eye protection/face protection. IF ON SKIN: Wash with plenty of soap and water. If skin irritation or rash occurs: Get medical advice/attention. Wash contaminated clothing before reuse. Dispose of contents and container in accordance with all local, regional, and national regulations.
Contains: reaction mass of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl- 2H-isothiazol-3-one (3:1); ADVIA Centaur IL6 Solid Phase, Lite Reagent, Calibrators, Quality Control.

CAUTION

This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

Contains sodium azide as a preservative. Sodium azide can react with copper or lead plumbing to form explosive metal azides. On disposal, flush reagents with a large volume of water to prevent buildup of azides. Disposal into drain systems must be in compliance with prevailing regulatory requirements.

Dispose of hazardous or biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with prevailing regulatory requirements.

Preparing Reagents

All reagents are liquid and ready to use. Remove all reagents from the refrigerator, and mix all primary reagent packs by hand. Visually inspect the bottom of the reagent packs to ensure that all particles are dispersed and resuspended before loading them onto the system. For detailed information about preparing the reagents for use, refer to the system operating instructions.

Note

- Discard reagent packs at the end of the on-system stability interval.
- Do not use reagents beyond the expiration date.

Storing and Stability

Store ADVIA Centaur IL6 reagent packs upright at 2–8° C away from heat and light sources. Reagent packs loaded on the system are protected from light. Reagents are stable at 2–8° C until the expiration date on the product.

Store ADVIA Centaur IL6 Calibrators at 2–8° C. Calibrators are stable at 2–8° C until the expiration date on the product.

Do not use ADVIA Centaur materials beyond the expiration date printed on the

product. For onboard stability, refer to *On-System Stability.*

Specimen Collection and Handling

This assay has been validated for use with serum and plasma (potassium EDTA, lithium heparin) samples.

Collecting the Specimen

- Collect all blood samples observing universal precautions for venipuncture.
- Handle all specimens as if capable of transmitting disease.
- Serum and plasma can be collected using recommended procedures for collection of diagnostic blood specimens by venipuncture.[1]
- Follow the instructions provided with your specimen collection device for use and processing.[2]
- Complete clot formation should take place before centrifugation.
- Centrifuge specimens as soon as possible with a maximum limit of two hours from the time of collection.[3]
- Keep tubes stoppered at all times.
- Do not use specimens with apparent contamination.

Storing the Specimen

- Separated specimens are stable for 5 hours at room temperature, 24 hours at 2–8° C. For longer storage, specimens may be frozen for 1 month at -20° C or colder. Avoid more than 3 freeze/thaw cycles. Do not store in a frost-free freezer.
- Thoroughly mix all thawed samples and centrifuge before testing.

The purpose of handling and storage information is to provide guidance to users. It is the responsibility of the individual laboratory to use all available references and/or its own studies when establishing alternative stability criteria to meet specific needs.

Transporting the Specimen

- Package and label specimens for shipment in compliance with applicable federal and international regulations covering the transport of clinical specimens and etiological agents.
- Store specimens stoppered at 2–8° C upon arrival.
- If shipment is expected to exceed 2 days, ship specimens frozen.

Procedure

Materials Provided

The following materials are provided:

REF	Contents	Number of Tests
10995080	1 ReadyPack primary reagent pack containing ADVIA Centaur IL6 Lite Reagent and Solid Phase 1 vial of lyophilized ADVIA Centaur IL6 low calibrator CAL L 1 vial of lyophilized ADVIA Centaur IL6 high calibrator CAL H ADVIA Centaur IL6 Master Curve card ADVIA Centaur IL6 Calibrator Assigned Value card	100

Materials Required but Not Provided

The following materials are required to perform this assay, but are not provided:

Item	Description		
REF 10699211	ADVIA Centaur Ancillary Probe (for ADVIA Centaur CP system	Was 3 APW 3 h only)	2 ReadyPack ancillary reagent packs containing 25.0 mL/pack
REF 01137199	ADVIA Centaur Wash 1		2 x 1500 mL/pack
REF 03773025	ADVIA Centaur Wash 1		2 x 2500 mL/pack

Optional Materials

The following materials may be used to perform this assay, but are not provided:

Item	Description	
REF 10995083	ADVIA Centaur IL6 Quality Control	1 x 7.0 mL control 1 CONTROL 1 1 x 7.0 mL control 2 CONTROL 2 1 x 7.0 mL control 3 CONTROL 3
	ADVIA Centaur IL6 QC assigned value sheet	
REF 10492364	ADVIA Centaur Multi-Diluent 13	2 ReadyPack ancillary reagent packs containing 10.0 mL/pack M-DIL

Preparing the Samples

This assay requires 50 µL of sample for a single determination. This volume does not include the unusable volume in the sample container, or the additional volume required when performing duplicates or other tests on the same sample. For detailed information about determining the minimum required volume, refer to the system operating instructions.

Before placing samples on the system, ensure that samples have the following characteristics:

- Samples are free of fibrin or other particulate matter. Remove particulates by centrifugation.
- Samples are free of bubbles or foam.

Preparing the System

Ensure that the system has sufficient primary reagent packs. For detailed information about preparing the system, refer to the system operating instructions.

Load the ReadyPack primary reagent packs in the primary reagent compartment using the arrows on the packs as a placement guide. The system automatically mixes the primary reagent packs to maintain homogeneous suspension of the reagents. For detailed information about loading reagents, refer to the system operating instructions.

Assay Procedure

The system automatically performs the following steps.

1. Dispenses 50 µL of sample into a cuvette.
2. Dispenses 140 µL of Solid Phase and 100 µL of Lite Reagent, then incubates for 7.5 minutes at 37° C on the ADVIA Centaur XP/XPT systems and 9.7 minutes at 37° C on the ADVIA Centaur CP system.
3. Separates the Solid Phase from the mixture, aspirates the unbound reagent, and washes the cuvettes with ADVIA Centaur Wash 1.
4. Dispenses 300 µL each of ADVIA Centaur Acid Reagent and ADVIA Centaur Base Reagent to initiate the chemiluminescent reaction.
5. Reports results.

On-System Stability

The ADVIA Centaur IL6 assay reagents are stable unopened until the expiration date on the product or onboard the system for 28 days. Discard reagent packs at the end of the 28-day on-system stability interval. Do not use reagents beyond the expiration date.

Reagent packs loaded on the system are protected from light.

The ADVIA Centaur IL6 calibrators are stable unopened until the expiration date on the product or onboard the system for 8 hours. For opened bottle stability, refer to *Reagents.*

Performing Calibration

For calibration of the ADVIA Centaur IL6 assay, use ADVIA Centaur IL6 Calibrators provided with each kit.

Note The low and high calibrators provided in this kit are matched to the ReadyPack primary reagent pack. Do not mix calibrator lots with different lots of reagent packs.

Each lot of calibrators contains a lot-specific Calibrator Assigned Value card to facilitate entering the calibration values on the system. Enter the values using the barcode scanner or the keyboard. For detailed information about entering calibrator values, refer to the system operating instructions.

Preparing the Calibrators

Prepare calibrators using the following steps:

1. Add 2.0 mL of reagent water into each calibrator vial using a volumetric or precision pipet.

Note For information about reagent water, refer to the systems operating instructions.

2. Invert the vials 5 times and let the calibrators stand for 30 minutes at room temperature to allow the lyophilized material to dissolve.
3. Gently swirl and invert the vials until homogeneous. Do not vortex.

Performing the Calibration

Perform the calibration procedure using the following steps:

1. Ensure that the calibrator values are entered on the system.
2. Ensure that the appropriate master curve values are entered on the system as needed, Refer to *Defining Master Curve Values.*
3. Ensure that the required reagents are loaded for the assay.
4. Schedule the calibrators to the worklist.
5. Label 2 sample cups with calibrator barcode labels: 1 cup for the low calibrator and another cup for the high calibrator.

Note Place the barcode label on the sample cup with the readable characters oriented vertically.

Note Calibrator barcode labels are lot-number specific. Do not use barcode labels from one lot of calibrators with any other lot of calibrators.

6. Gently mix the low and high calibrators and dispense at least 270 µL into the appropriate sample cups. Avoid bubbles.

Note This procedure uses calibrator volumes sufficient to measure each calibrator in duplicate.

7. Load the calibrator sample cups in a rack.
8. Place the rack in the sample entry queue.
9. Start the entry queue, if required.

Note Dispose of any calibrator remaining in the sample cups after 8 hours. Do not return any calibrators back into the vials after calibration because evaporation can occur, which may affect performance. Do not refill sample cups when the contents are depleted; if required, dispense fresh calibrators.

Calibration Frequency

Calibrate the assay at the end of the 14-day calibration interval. Additionally, the ADVIA Centaur IL6 assay requires a two-point calibration:

- When changing lot numbers of primary reagent packs.
- When replacing system components.
- When quality control results are repeatedly out of range.

Defining Master Curve Values

The ADVIA Centaur IL6 assay requires you to enter Master Curve values when using a new reagent lot number. For each new lot number of Lite Reagent and Solid Phase, use the barcode reader or keyboard to enter the Master Curve values on the system. The Master Curve card contains the Master Curve values. For information about entering calibration values, refer to the system operating instructions.

Performing Quality Control

Follow government regulations or accreditation requirements for quality control frequency. To monitor system performance and chart trends, as a minimum requirement, assay 3 levels of quality control material with known IL-6 concentrations on each day that samples are analyzed. Test quality control samples after performing a two-point calibration. Treat all quality control samples the same as patient samples.

Siemens Healthcare Diagnostics recommends the use of ADVIA Centaur Interleukin-6 (IL6) Quality Control or an equivalent commercially available control material with at least 3 levels. A satisfactory level of performance is achieved when the analyte values obtained are within the acceptable control range for the system or within your range, as determined

by an appropriate internal laboratory quality control scheme.

For detailed information about how to enter quality control values, refer to the system operating instructions.

Refer to the assigned value sheet for the suggested target values and ranges specific for the lot number of the controls.

Follow your laboratory internal QC procedures if the results obtained are outside acceptable limits.

Sample results are invalid and must be repeated if the controls are out of range.

Preparing the Quality Control Material

Prepare quality control material using the following steps:

1. Add 7.0 mL of reagent water into each vial using a precision pipet. Replace cap.

   Note For information about reagent water requirements, refer to the system online help.

2. Invert the vials 5 times and let the controls stand for 30 minutes at room temperature to allow the lyophilized material to dissolve.
3. Gently swirl and invert the vials to ensure homogeneity of the material. Do not vortex.

Note Use quality control material within the stability limits specified in *Reagents* and discard any remaining material.

Quality Control Procedure

Perform the quality control procedure using the following steps:

1. Ensure that the quality control definitions are defined, and that the quality control values are entered on the system using the assigned value sheet provided.
2. Load the required reagents for the assay.
3. Schedule the quality control material.
4. Label sample containers with barcode labels: one container for the level 1 control, and one container for the level 2 control, and one container for the level 3 control. Place the barcode labels on the sample containers with the readable characters oriented vertically.

Note Barcode labels are lot-specific. Do not use barcode labels from one lot of controls with any other lot of controls.

5. Dispense a sufficient amount of each quality control into the appropriate sample containers. Avoid bubbles.
6. Load the samples according to the system operating instructions.

Note Dispose of any quality control material that remains in the sample container after 8 hours. Do not refill or reuse sample containers. Do not return any quality control material back into the original container.

Taking Corrective Action

If the quality control results do not fall within the suggested target values and ranges or within the laboratory's established values, do not report results.

- Verify that the materials are not expired.
- Verify that required maintenance was performed.
- Verify that the assay was performed according to the instruction for use.
- Rerun the assay with fresh quality control samples.

Perform corrective actions in accordance with your established laboratory protocol. If necessary, contact your local technical support provider or distributor for assistance.

Results

Calculation of Results

For detailed information about how the systems calculate results, refer to the system operating instructions.

The system reports IL-6 results in pg/mL.

The ADVIA Centaur systems will display results below the Limit of Quantitation (LoQ) of 3.0 pg/mL. These results are considered below the sensitivity of the assay and should be reported as < 3.0 pg/mL.

Dilutions

The following information pertains to dilutions:

- Results below the measuring interval are reported as < 3.0 pg/mL. Results above the measuring interval (> 5500.0 pg/mL) require dilution to obtain an accurate result.
- Patient samples can be automatically diluted by the system using ADVIA Centaur Multi-Diluent 13.
- For automatic dilutions, ensure that the ADVIA Centaur Multi-Diluent 13 is loaded. Enter a Dilution Point ≤ 5500.0 pg/mL. To define a dilution factor, refer to the following table:

Sample	Dilution	Sample Volume
ADVIA Centaur XP and ADVIA Centaur XPT	1:10	50 µL
ADVIA Centaur CP	1:2	100 µL

For detailed information about automatic dilutions, refer to the system operating instructions. Ensure that the results are mathematically corrected for dilution. If a dilution factor is entered when scheduling the test, the system automatically calculates the results.

Limitations

The following information pertains to limitations of the assay:

- The performance of the ADVIA Centaur IL6 assay has not been established with matrices other than serum or plasma.
- Do not use heat-inactivated specimens.
- The performance of the assay has not been established for populations of immunocompromised or immunosuppressed patients.
- Heterophilic antibodies in human serum and plasma can react with the immunoglobulins included in the assay components causing interference with *in vitro* immunoassays.[4] Samples from patients routinely exposed to animals or animal serum products can demonstrate this type of interference, which can potentially cause an anomalous result. Additional information may be required for diagnosis.
- Do not use ADVIA Centaur IL6 test results interchangeably with test results from other IL-6 assays.
- Results of this assay should always be interpreted in conjunction with the patient's medical history, clinical presentation, and other findings.

Conditions of Authorization for the Laboratory

The ADVIA Centaur IL6 assay Letter of Authorization, along with the authorized Fact Sheet for Healthcare Providers, the authorized Fact Sheet for Patients, and authorized labeling are available on the FDA website:

https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

However, to assist clinical laboratories using the ADVIA Centaur IL6 assay, the relevant Conditions of Authorization are listed below:

- Authorized laboratories[a] using the ADVIA Centaur IL6 assay will include with result reports of the assay, all authorized Fact Sheets. Under exigent circumstances, other appropriate methods for disseminating these Fact Sheets may be used, which may include mass media.
- Authorized laboratories using the ADVIA Centaur IL6 assay will use the product as outlined in the Instructions for Use. Deviations from the authorized procedures, including the authorized instruments, authorized clinical specimen types, authorized control materials, authorized other ancillary reagents and authorized materials required to use the
  ADVIA Centaur IL6 assay are not permitted.
- Authorized laboratories that receive the ADVIA Centaur IL6 assay will notify the relevant public health authorities of their intent to run the assay prior to initiating testing.
- Authorized laboratories using the ADVIA Centaur IL6 assay will have a process in place for reporting test results to healthcare providers and relevant public health authorities, as appropriate.
- Authorized laboratories will collect information on the performance of the ADVIA Centaur IL6 assay and report to DIHD/OHT7-OIR/OPEQ/ CDRH (via email: CDRH EUA Reporting@fda.hhs.gov) and Siemens Healthineers Technical Support (https://www.siemens-healthineers.com/en-us/; tel: 1.877.229.3711) any suspected occurrence of false reactive or false nonreactive results and significant deviations from the established performance characteristics of the assay of which they become aware.
- All laboratory personnel using the ADVIA Centaur IL6 assay must be appropriately trained in automated immunoassay techniques and use appropriate laboratory and personal protective equipment when handling this kit, and use the ADVIA Centaur IL6 assay in accordance with the authorized labeling. All laboratory personnel using the assay must also be trained in and be familiar with the interpretation of results of the ADVIA Centaur IL6 assay.
- Siemens Healthineers, authorized distributors, and authorized laboratories using the ADVIA Centaur IL6 assay will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

[a] The letter of authorization refers to, “Laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform moderate or high complexity tests” as “authorized laboratories.”

Expected Values

The ADVIA Centaur IL6 assay results were obtained on 139 apparently healthy males (n = 83) and females (n = 56) using the ADVIA Centaur XP system. The age range was 21–67 years. The reference interval up to 4.4 pg/mL (97.5th percentile) was determined according to CLSI Document EP28-A3c.[5] Normally, IL-6 is not detected in the blood or is present in low quantities.

As with all *in vitro* diagnostic assays, each laboratory should determine its own reference range(s) for the diagnostic evaluation of patient results. Consider these values as

guidelines only.

Clinical Assessment

Cut-off Determination

Samples from confirmed COVID-19 patients who presented at US hospital Emergency Departments (ED) were used to derive an assay cut-off value that was predictive of the need for intubation with mechanical ventilation. The cut-off value for the ADVIA Centaur IL6 assay was determined with the ADVIA Centaur XP system, using samples from 200 SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) confirmed-positive COVID-19 patients. A receiver operating characteristic (ROC) curve was used to determine a cut-off value of 35 pg/mL that yielded an optimal balance of sensitivity and specificity.

Clinical Performance

Samples were selected from patients with symptomatic PCR-confirmed COVID-19, who presented to a hospital Emergency Department (ED) in Northern California in the United States between April and June, 2020.

Of the total of 136 patients included in the clinical performance analysis, 35 patients subsequently underwent intubation with mechanical ventilation, and 101 were not intubated during their hospitalization.

	Mechanical Ventilation	
	Yes	**No**
IL6 ≥ 35 pg/mL	30	36
IL6 < 35 pg/mL	5	65
Sensitivity	85.7% (95% CI = 70.6% to 93.7%)	
Specificity		64.4% (95% CI = 54.6% to 73.0%)

- Positive predictive value: 45.5% (95% CI = 34.0% to 57.4%)
- Negative predictive value: 92.9% (95% CI = 84.3% to 96.9%)
- Prevalence of intubation with mechanical ventilation: 25.7% (35/136).

Results and Interpretation

PCR-confirmed COVID-19 patients that have an ADVIA Centaur IL-6 concentration ≥ 35 pg/mL at presentation are at increased risk for intubation with mechanical ventilation during their hospitalization. IL-6 values should be used in conjunction with clinical findings and the results of other laboratory parameters. IL-6 values alone are not indicative of the need for intubation with mechanical ventilation.

Performance Characteristics

The ADVIA Centaur XP, ADVIA Centaur XPT, and ADVIA Centaur CP systems use the same reagent formulation. Performance characteristics information represent data from the ADVIA Centaur XP system, unless otherwise noted.

Measuring Interval

The ADVIA Centaur IL6 assay measures interleukin-6 concentrations from 3.0–5500.0 pg/mL.

Specificity

The ADVIA Centaur IL6 assay shows minimal cross-reactivity (< 1.0%) with interleukin-1 α, interleukin-1ß, interleukin-2, interleukin-3, interleukin-4, interleukin-8, IL-6 soluble

receptor, interferon-ϒ, interferon- α , interferon-ß, tumor necrosis factor- α and tumor necrosis factor-ß.

Cross-reactivity was tested in the presence (~10 pg/mL) and absence of IL-6 according to CLSI Document EP7-A2[6] using the ADVIA Centaur IL6 assay.

Percent cross-reactivity is calculated as:

$$\% \text{ cross-reactivity} = \frac{(\text{concentration of spiked sample} - \text{concentration of unspiked sample})}{\text{concentration of cross-reactant}} \times 100$$

The following cross-reactants were tested:

Substance	Substance Test Concentration	Analyte Concentration (pg/mL)	Cross-reactivity (%)
Interleukin-1 α	50 ng/mL	≤ LoQ 7.2–8.7	ND[a] 0.003%
Interleukin-1ß	50 ng/mL	≤ LoQ 7.2–8.7	ND 0.004%
Interleukin-2	50 ng/mL	≤ LoQ 7.2–8.7	ND 0.003%
Interleukin-3	50 ng/mL	≤ LoQ 7.2–8.7	ND 0.002%
Interleukin-4	50 ng/mL	≤ LoQ 7.2–8.7	ND 0.003%
Interleukin-8	50 ng/mL	≤ LoQ 7.2–8.7	ND 0.004%
IL-6 soluble receptor	50 ng/mL	≤ LoQ 7.2–8.7	ND 0.004%
Interferon-ϒ	50 ng/mL	≤ LoQ 7.2–8.7	ND 0.001%
Interferon- α	50 ng/mL	≤ LoQ 7.2–8.7	ND 0.005%
Interferon-ß	50 ng/mL	≤ LoQ 7.2–8.7	ND 0.001%
Tumor necrosis factor- α	50 ng/mL	≤ LoQ 7.2–8.7	0.001% 0.004%
Tumor necrosis factor- ß	50 ng/mL	≤ LoQ 7.2–8.7	0.001% 0.005%

[a] Not detected

Detection Capability

The limit of blank (LoB), limit of detection (LoD), and the limit of quantitation (LoQ) were determined as described in CLSI Document EP17-A2.[7]

The LoB is defined as the highest measurement result that is likely to be observed for a blank sample. The ADVIA Centaur IL6 assay has an LoB of 1.3 pg/mL.

The LoD is defined as the lowest concentration of IL-6 that can be detected with 95% probability. The ADVIA Centaur IL6 assay has an LoD of 2.7 pg/mL.

The LoQ is defined as the lowest concentration of IL-6 that can be detected at a total error of 45%. The ADVIA Centaur IL6 assay has an LoQ of 3.0 pg/mL.

Report results below the LoQ as < 3.0 pg/mL.

Precision

Precision was evaluated according to the CLSI protocol EP5-A3.[8]

Four serum precision samples were prepared with IL-6 concentrations spanning the measuring interval. Samples were tested in replicates of 2 in 2 runs per day over 20 days, yielding

80 observations per sample.

Specimen Type	N	Mean (pg/mL)	Repeatability (Within-Run) SD (pg/mL)	Repeatability (Within-Run) CV (%)	Within-Lab (Total) SD (pg/mL)	Within-Lab (Total) CV (%)
Sample 1	80	5.6	0.54	9.6	0.56	10.0
Sample 2	80	13.0	0.55	4.2	0.64	5.0
Sample 3	80	187.7	6.00	3.2	6.54	3.5
Sample 4	80	4568.9	80.51	1.8	121.21	2.7

Specimen Collection Comparison

The ADVIA Centaur IL6 assay was evaluated using different serum and plasma matrices. Passing-Bablok regression and a Pearson coefficient analysis were performed and no significant difference between tube types was observed. The following results were obtained:

Serum vs	n	Slope	Intercept	r	Sample Interval (pg/mL)
Potassium EDTA plasma	66	1.00	1.06	0.98	3.1–1266.5
Lithium heparin plasma	57	0.97	0.15	0.99	3.4–1266.5
Plasma gel-barrier tube	57	0.96	-0.72	0.99	3.4–1266.5
Serum gel-barrier tube	76	1.04	-1.33	1.00	3.6–5268.9

Interferences

Interfering substances at the levels indicated in the table below were tested as described in CLSI Document EP7-A2[6] using the ADVIA Centaur IL6 assay.

Substance	Substance Test Concentration Common Units (SI Units)	Analyte Concentration (pg/mL)	Bias (%)
Hemoglobin	1000 mg/dL (0.62 mmol/L)	8.4–10.6	-10%
		99.8–123.4	-9%
Bilirubin, conjugated	25 mg/dL (427.5 µmol/L)	8.4–10.6	10%
		99.8–123.4	-2%
Bilirubin, unconjugated	60 mg/dL (1026 µmol/L)	8.4–10.6	-7%
		99.8–123.4	-9%
Lipemia (Intralipid)	1500 mg/dL (17.0 mmol/L)	8.4–10.6	8%
		99.8–123.4	4%

Two levels of IL-6 were tested with each of the following substances at the levels indicated, and caused no significant interference in the ADVIA Centaur IL6 assay at IL-6 concentrations of 8.8–13.9 pg/mL and 106.8–277.8 pg/mL.

Substance	Substance Test Concentration Common Units (SI Units)	Analyte Concentration (pg/mL)	Bias (%)
Cholesterol	500 mg/dL (12.95 mmol/L)	8.8–13.9	4%
		106.8–277.8	-1%
Human gamma globulins	5 g/dL (50 g/L)	8.8–13.9	-9%
		106.8–277.8	-3%
Total protein	12 g/dL (120 g/L)	8.8–13.9	6%
		106.8–277.8	1%
Rheumatoid factor	500 IU/mL	8.8–13.9	-3%
		106.8–277.8	-5%
Triglycerides	1500 mg/mL (17.0 mmol/L)	8.8–13.9	-9%
		106.8–277.8	7%

Linearity

Linearity was evaluated according to the CLSI protocol EP6-A.[22] Human serum samples were spiked with recombinant IL-6 and then mixed with analyte-free, human serum matrix. The resulting serum pools were assayed for IL-6.

Sample	Range (pg/mL)	Slope		Intercept		R^2	Recovery Range (pg/mL)
		Point	95% CI	Point	95% CI		
1	1.3–5548.1	0.95	0.93–0.97	0.07	-0.29 – 0.42	1.000	93.1% to 96.7%
2	3.5–110.9	0.97	0.94–1.01	-0.57	-1.32 – 0.18	0.997	85.4% to 102.5%

The ADVIA Centaur IL6 assay is linear from 3.0–5500.0 pg/mL.

Dilution Recovery

Five samples containing high levels of IL-6 (6363.8–6741.9 pg/mL) were diluted 1:10 with ADVIA Centaur Multi-Diluent 13 using the ADVIA Centaur XP system (1-part sample plus 9-parts diluent). The observed percent recovery for individual samples ranged from 103%–108%.

On the ADVIA Centaur CP system, five samples containing high levels of IL-6 (4249.5–7418.2 pg/mL) were diluted 1:2 with ADVIA Centaur Multi-Diluent 13 (1-part sample plus 1-part diluent). The observed percent recovery for individual samples ranged from 105%–120%.

The samples were assayed for recovery and parallelism, correcting the diluted sample by the dilution factor.

High-Dose Hook Effect

Patient samples with high IL-6 levels can cause a paradoxical decrease in the Relative Light Units (RLUs) (high-dose hook effect). In the ADVIA Centaur IL6 assay, patient samples with IL-6 levels as high as 233,065.6 pg/mL will assay greater than 5500.0 pg/mL.

Instrument Comparison

A comparison of the ADVIA Centaur XP, ADVIA Centaur XPT, and ADVIA Centaur CP systems was performed in accordance with CLSI Document EP9-A3.[10]

ADVIA Centaur XPT

The relationship of the ADVIA Centaur IL6 assay using the ADVIA Centaur XPT system (y) and the ADVIA Centaur XP System (x) is described using Passing-Bablok regression and a Pearson coefficient. A total of 148 serum samples with IL-6 concentrations in the range of 4.4–4507.4 pg/mL were tested:

ADVIA Centaur IL6 (y) = 0.97 (x) + 1.36 pg/mL (intercept), r = 1.00.

ADVIA Centaur CP

The relationship of the ADVIA Centaur IL6 assay using the ADVIA Centaur CP system (y) and the ADVIA Centaur XP system (x) is described using Passing-Bablok regression and a Pearson coefficient. A total of 138 serum samples with IL-6 concentrations in the range of 3.2–5250.9 pg/mL were tested:

ADVIA Centaur IL6 (y) = 0.96 (x) + 0.38 pg/mL (intercept), r = 1.00.

Standardization

The ADVIA Centaur IL6 assay is standardized to an internal standard that is traceable to the World Health Organization (WHO) 1st International Standard for INTERLEUKIN-6 (IL-6, Human rDNA derived), NIBSC code 89/548. Assigned values for calibrators are traceable to this standard.

Technical Assistance

For customer support, please contact your local technical support provider or distributor. siemens-healthineers.com

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10. Clinical and Laboratory Standards Institute. *Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition.* Wayne, PA: Clinical and Laboratory Standards Institute; 2013. CLSI Document EP9-A3.

Definition of Symbols

The following symbols may appear on the product labeling:

Symbol	Definition	Symbol	Definition
IVD	*In vitro* diagnostic medical device	REF	Catalog number
	Legal manufacturer	EC REP	Authorized Representative in the European Community
CE	CE Mark	CE 0088	CE Mark with identification number of notified body
	Consult instructions for use		Biological risk
	Do not freeze (> 0° C)		Temperature limitation
	Lower limit of temperature		Upper limit of temperature
	Keep away from sunlight and heat		Up
	Use by	Σ (n)	Contains sufficient for (n) tests
LOT	Batch code		Shake the reagent pack vigorously. Refer to Preparing Reagents in the assay specific ADVIA Centaur product instructions for detailed information.
YYYY-MM-DD	Date format (year-month-day)	Rev.	Revision
MC TDEF	Master Curve Definition	CHECKSUM	Variable hexadecimal number that ensures the Master Curve and Calibrator definition values entered are valid.
LOT DTL	Lot Details	PRINTED WITH SOY INK	Printed with soy ink
	Recycle	RxOnly	Prescription use only

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