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# How Websites and Mobile Applications Wrongly Calculate eGFR by MDRD Equation

Muhamad Ali Alherk[1*], Mohammad Ammar M. K. Yahia[2], Kaumudi Bery[3]

[1]Muaither Health Center, Diagnostic Laboratory, Primary Health Care Corporation (PHCC), Doha, Qatar, **ORCID ID:** 0000-0003-2188-4952
[2]Al Wakra (South) Health Center, Diagnostic Laboratory, Primary Health Care Corporation (PHCC), Doha, Qatar, **ORCID ID:** 0000-0002-9588-4851
[3]Al Ruwais Health Center, Diagnostic Laboratory, Primary Health Care Corporation (PHCC), Doha, Qatar, **ORCID ID:** 0000-0001-8061-6718

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***Corresponding author:** Muhamad Ali Alherk
Muaither Health Center, Diagnostic Laboratory, Primary Health Care Corporation (PHCC), Doha, Qatar

**Abstract** **Review Article**

Equations to estimate glomerular filtration rate (GFR) are routinely used for the diagnosis and classification of chronic kidney diseases (CKDs). Modification of Diet in Renal Disease (MDRD) equation is an old one and has been replaced in many countries by CKD Epidemiology Collaboration (CKD-EPI) equation, but MDRD is still available in routine practice worldwide, especially in developing countries. Many users of MDRD, don't know that it has two different versions (equations). This idea makes confusion in practice and affected the developers of this equation in internet websites and mobile applications. In this review, we will focus on this dilemma and try to solve it by explaining the basics of these two versions, and when I can choose each version, then the reflection of this issue on about 105 websites/Applications from different countries around the world. After that, we will give recommendations for both developers and seekers of this equation about overcoming this debate.

**Keywords**: MDRD – GFR – chronic kidney diseases – estimated Glomerular Filtration rate – calculator.



## INTRODUCTION

eGFR equations are considered as one of the cornerstones in the assessment of renal functions, by using simple laboratory tests (usually serum creatinine), plus a few demographic information like sex, and age [1].

MDRD is an old eGFR equation, but it is still available internationally [1-3]. Mainly there are two versions of this equation: before and after the creatinine standardization program, and both versions give different results for the same patient.

On the other hand, MDRD needs special software like a website or a mobile application for calculation. Many of these resources have failed to clarify the difference between the two versions of MDRD, and how this difference can affect the patient renal functions assessment and management. We will address this issue and how can be prevented. In this retrospective, we will explain the differences between these two equations and when we can use each one.

### Creatinine versus eGFR in renal function assessment

Serum creatinine is the main laboratory test used in the assessment of renal functions, but usually, it is affected by several factors such as age, sex, creatinine production in muscles, dietary intake of creatinine, extra-renal clearance of creatinine in the gastrointestinal tract, and tubular secretion of creatinine [4]. All these factors were the basis of developing GFR equations, to improve the predictive value of serum creatinine. Many trials started in the 1970s [5], and the only one available till now is the Cockroft-Gault equation, which is still in use in special situations, but many other equations didn't survive for many reasons. Starting in the 21st century, international guidelines started recommending various newer eGFR equations like MDRD or the more recent CKD-EPI for the assessment of renal functions.

### MDRD Story

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) began a multicenter study named the Modification of Diet in Renal Disease (MDRD). It was designed to assess the

acceptance, safety, and efficacy of restricted protein and phosphorus diets in patients with chronic renal disease [6, 7]. One of the results of this study is the development of the MDRD equation.

The original MDRD equation had been announced in 1999 and developed based on 6 variables: serum creatinine, age, sex, ethnicity, and serum levels of urea and albumin (Table 1 – equation No. 1) [8]. Subsequently, in 2000 a simplified equation including 4 variables had been proposed to simplify its clinical use, and it was consisting of age, sex, ethnicity, and serum creatinine (Table 1 – equation No. 2) [9]. After the great work on the creatinine standardization program (see below), it was necessary to re-express the MDRD equation to fulfill the new development. Then the updated MDRD equation has been announced in 2006 (Table 1 – equation No. 3) [10].

**Table 1: The different versions of the MDRD equation**

| No. | Equation Name | Year | The equation details |
|---|---|---|---|
| **1** | Original MDRD (6 Variables) [5] | 1999 | **Equation No.1**: GFR = 170 x $(Scr^{a})^{-0.999}$ x $(Age)^{-0.176}$ x [0.762 if patient is female] x [1.180 if patient is black] x $[SUN^{b}]^{-0.170}$ x $[Alb]^{+0.318}$ |
| **2** | Simplified MDRD (4 Variables) [6] | 2000 | **Equation No.2**: eGFR (ml/min/1.73m$^2$) = 186 x $[Scr]^{-1.154}$ x $[Age]^{-0.203}$ x [0.742 if female] x [1.21 if black] |
| **3** | Updated MDRD (4 Variables, and Standardized creatinine) [7] | 2006 | **Equation No.3**: eGFR (ml/min/1.73m$^2$) = 175 x $[Scr]^{-1.154}$ x $[Age]^{-0.203}$ x [0.742 if female] x [1.21 if black] |

[a]Scr = Serum Creatinine – [b]SUN = Serum Urea Nitrogen.

**International Versions of MDRD**

The original MDRD equation (equation No. 1 in Table 1) was not used in the international recommendations and hence we will not be discussing the same here. In many countries, many research papers have been published on the accuracy of the MDRD equation. Particularly in Asia, there has been a lot of research like those published in India [11, 12], China [13], Japan [14], and Pakistan [15]. Few of these researchers have added special racial factors to equations 2 and 3 in table 1. Also, they were ignored in our work, because they were not adopted and applied to websites/mobile applications globally.

The focus internationally was on equations 2 and 3 in table 1, and the only difference between both equations is the factor, which is 186 for equation 2, and 175 for equation 3. In the rest of this review, we will use the shortcut simplified MDRD for equation 2, and updated MDRD for equation 3.

**The importance of the creatinine standardization program (from a laboratory perspective)**

In 2006 the National Kidney Disease Education Program (NKDEP) created a Laboratory Working Group in collaboration with the International Federation of Clinical Chemistry (IFCC) and the European Communities Confederation of Clinical Chemistry (now called the European Federation of Clinical Chemistry and Laboratory Medicine). One of the main activities of this workgroup is creating a creatinine standardization program. NKDEP has been stopped in 2019, and NIDDK has carried forward the promotion activities developed under NKDEP's program to meet the ongoing need [16].

The NIDDK Laboratory Working Group was created to reduce inter-laboratory variation in creatinine assay calibration and therefore enable more accurate estimates of glomerular filtration rate (eGFR), and to prepare recommendations to standardize and improve creatinine measurement. Its work was published in 2006 [17].

To achieve its goals, this group has recommended the use of reference materials (calibrators) that are traceable to a reference method called Isotope Dilution Mass Spectrometry (IDMS) by all manufacturers of creatinine reagents. In this way, we can expect theoretically that the same specimen will give the same result in any laboratory around the world.

The best clinical implications of this program are improving the estimation of GFR equations and appropriate adjustment of medications in patients with low GFR values [18]. One of the main recommendations of this group to the clinical laboratories is to use a validated IDMS-traceable equation like updated MDRD and CKD-EPI, as the simplified MDRD, will give higher estimated GFR values compared to the recommended equations [19]. Now and after 16 years of starting this program, the majority of commercial companies that manufacture creatinine reagents have standardized their methods.

**The importance of the MDRD equation in the international recommendations**

MDRD like other eGFR equations has two benefits in general; help in the staging of Chronic Kidney Diseases (CKD), assessment of renal functions of the potential kidney donors [1], and adjustment of drug dosing in renal impairment cases [20-22]. Kidney Disease Outcomes Quality Initiative (K/DOQI) was the first organization that recommended using the simplified MDRD equation in clinical practice in 2002 [5], and after introducing the creatinine standardization

program in 2006 [17], many guidelines (other than mentioned above) have recommended and/or accepted the updated MDRD equation [1-3, 23-29].

On the other side, many guidelines have shifted to recommend the CKD-EPI equation [30-33], as it is more accurate in the higher eGFR values (more than 60 ml/min/1.73 $m^2$) [34], and had been tested with patients older than 70 years [35], compared to MDRD age criteria of (18 – 70 years old) [7]. However, the lack of application creatinine standardization globally is complicating following this recommendation in routine practice, as there are many countries not established yet this process, so for these countries, the MDRD is still available widely (as the CKD-EPI equation is not valid for old creatinine methods), also MDRD in the last 16 years has been used in many international studies, which revealed in many recommendations, that why it is early to ignore it worldwide.

**The expression of MDRD in Internet websites/mobile applications**

In practice, the MDRD equation is available in many laboratories and is still used widely around the world, especially in developing countries. The traditional calculators are unable to calculate the MDRD formula, so special software is needed (like a website or mobile application).

We have reviewed about 105 resources including international websites, and mobile applications (mainly android versions). In case the developer is the same in both website and mobile application (for example Medscape website and Mobile application), we have considered them two different resources. The search of resources was done by Google search engine for websites, and Google Play for Android applications and we could reach equations from different countries/languages around the world. To focus on the difference between the two versions of the MDRD equation, we agreed to choose a borderline example (case) with specific values as per Table 2. This case will be categorized as CKD stage 2 (G2) by using simplified MDRD, and CKD stage 3 (G3) by using the updated equation, which is diagnosed as chronic kidney disease.

**Table 2: The example used to check MDRD equations**

| Parameters | Old MDRD Value (Factor 186) | Updated MDRD Value (Factor 175) |
|---|---|---|
| Sex = Female,<br>Age = 50 Years,<br>Serum Creatinine = 1 mg/dl (88.4 µmol/L), and<br>Race = Non-African | 62.38 ml/min/1.73 $m^2$<br>(Accepted Values are: 62 & 63 ml/min/1.73 $m^2$) | 58.69 ml/min/1.73 $m^2$<br>(Accepted Values are: 58 & 59 ml/min/1.73 $m^2$) |
| CKD staging | CKD Stage 2 (G2) | CKD Stage 3a (G3a) |

Note: KDIGO guidelines define CKD as the persistence of a marker of kidney damage (like high albuminuria, urine sediment abnormalities …etc.) plus eGFR < 60 ml/min/1.73 $m^2$ for more than 3 months [1].

According to the above example, we have divided the 105 sites/applications into the following categories:

1. 20 resources (19%) expressed both results (58.69 and 62.38 ml/min/1.73 $m^2$), mentioning the IDMS traceability (Table 3).
2. 38 resources (36.2%) expressed IDMS results only (58.69 or 59 ml/min/1.73 $m^2$) using the updated MDRD equation, with or without mentioning the IDMS traceability (Table 4).
3. 47 resources (44.8%) expressed values ≥ 62 ml/min/1.73 $m^2$ using simplified MDRD equation (Table 5).

**Table 3: Websites/Mobile applications that give both simplified and updated MDRD values**

| No. | Website (Linked) /Mobile App. Name | Owner/Developer | Country |
|---|---|---|---|
| 1 | MSD Manuals | MSD/EBMcalc | USA |
| 2 | Merck Manuals | Merck/EBMcalc | USA |
| 3 | Nephron.org | Nephron Information Center/Touchcalc | USA |
| 4 | www.mdrd.com | Mdrd.com/Touchcalc | USA |
| 5 | TouchCalc.com | Touchcalc Inc. | USA |
| 6 | www.sfndt.org | Francophone Soc. Of Nephr, Dial Transpl. (SFNDT) | France |
| 7 | RenalGuard.com | RenalGuard | USA |
| 8 | www.senefro.org | SOCIEDAD ESPAÑOLA DE NEFROLOGÍA (Senefro) | Spain |
| 9 | www.sbn.org | Sociedade Brasileira de Nefrologia (SBN) | Brazil |
| 10 | www.renal.org.ar | Asociación Regional De diálisis Y Trasplantes Renales | Argentina |
| 11 | www.cnhm.ma | Centre de Néphrologie-Hémodialyse de Meknès (CNHM) | Morocco |
| 12 | www.CardioLink.it | CardioLink | Italy |
| 13 | https://boris.bikbov.ru | Omnibus rebus | Russia |
| 14 | www.nefrocalc.net | Nefrocalc Version 2.0 | Brazil |

| No. | Website (Linked) /Mobile App. Name | Owner/Developer | Country |
|---|---|---|---|
| 15 | arquivos.sbn.org.br | Universidade Federal de Mato Grosso do Sul/Nefrocalc 1.0 | Brazil |
| 16 | www.cbm25.fr | Center for Medical Biology | France |
| 17 | hpathy.com | Hpathy | India |
| 18 | www.ebmconsult.com | EBMConsult | USA |
| 19 | PharmCalc.com | PharmCalc | UK |
| 20 | PharmCalc® App. | | |

Last accessed on 2022 July 10.

**Table 4: Websites/Mobile applications that give updated MDRD values only**

| No. | Website (Linked) /Mobile App. Name | Owner/Developer | Country |
|---|---|---|---|
| 1 | Mdcalc.com | MDCalc | USA |
| 2 | MDCalc® App. | | |
| 3 | NIDDK (Conv. Units) | NIDDK | USA |
| 4 | hepatitisc.uw.edu | University of Washington | USA |
| 5 | hepatitisb.uw.edu | | |
| 6 | clincalc.com | ClinCalc LLC | USA |
| 7 | Columbiamedicine.org | Columbia University | USA |
| 8 | pathlabs.rlbuht.nhs.uk | Royal Liverpool Broadgreen University | UK |
| 9 | kidneyregistrylb.com | Lebanon Society of Nephrology and Hypertension | Lebanon |
| 10 | mdapp.co | MDApp | UK |
| 11 | GFR Calculator App. | MDApp+ | |
| 12 | Calculator.net | Calculator.net | USA |
| 13 | thecalculator.co | The Calculator .CO | NA[a] |
| 14 | globalrph.com | Global RPH | USA |
| 15 | easycalculation.com | Easycalculation.com | India |
| 16 | omnicalculator.com | Omni Calculator sp. | Poland |
| 17 | mdsaude.com | MD.Saúde | Spain |
| 18 | saomarcoslaboratorio.com.br | São Marcos Laboratorio | Brazil |
| 19 | ctinjection.com | CTinjection | France |
| 20 | bioltrop.fr | BIOLogie TROPicale | France |
| 21 | 360 medics App. | 360Medics | France |
| 22 | eGFR-NKF (old-2015) App. | eGFR-NKF (old-2015) Supported by Daiichi-Aankyo | USA |
| 23 | NKF KDOQI App. | NKF | USA |
| 24 | Medical Equations App. | Sanapps Dev | NA[a] |
| 25 | eGFR Calculators Pro App. | iMedical Apps | Indonesia |
| 26 | Pocket GFR Calculator App. | iMedical Apps | Indonesia |
| 27 | Renal Dose adjustment &Cr Cl App. | Apicel | Malaysia |
| 28 | NefroConsultor App. | Madilon Medical Care | NA[a] |
| 29 | CKD-EPI y MDRD UdelaR Hospital Uruguay App. | Alberto Hernandez | Uruguay |
| 30 | eGFR App. | Ksoft Apps | NA[a] |
| 31 | GFR Calculator App. | Mahmoud AbuZnaid | NA[a] |
| 32 | CalcuMed App. | Coder Gang | Peru |
| 33 | eGFR Calculator App. | Gumption Multimedia | Netherlands |
| 34 | Estimated GFR App. | Gumption Multimedia | Netherlands |
| 35 | Basic Medical Formulas (Calculations) App. | PharmaDON | NA[a] |
| 36 | Real eGFR App. | Rodrigo Sepulveda Palamara | Chile |
| 37 | Estimated GFR App. | Prof.Dr.Erdem Akbary | Turkey |
| 38 | GFR Easycalc App. | Dr. Louis Janssens | NA[a] |

[a]NA = Not available/Not Mentioned. Last accessed on 2022 July 10.

**Table 5: Websites/Mobile applications that give simplified MDRD values only**

| No. | Website (Linked) /Mobile App. Name | Owner/Developer | Country |
|---|---|---|---|
| 1 | Calculate by QxMD | QxMD Medical Software Inc. | USA |
| 2 | Calculate by QxMD App. | | |
| 3 | Medscape.com | Medscape® | USA |
| 4 | Medscape® App. | | |
| 5 | Guidelinecentral.com | GuidelineCentral | USA |
| 6 | Ukidney.com | Ukidney (Internet School of Nephrology) | U.K |
| 7 | Accessmedicina.mhmedical.com | Access Medicine (McGraw Hill) | USA/Mexico |
| 8 | Patient.info | Patient.info | UK |
| 9 | www.UPMC.com | University of Pittsburgh Medical Center | USA |

| No. | Website (Linked) /Mobile App. Name | Owner/Developer | Country |
|---|---|---|---|
| | | (UPMC) | |
| 10 | Nephron.com | Nephron.com | USA |
| 11 | www.scymed.com | MediCalc (SkyMed Inc.) | USA |
| 12 | eGFR (Skymed) App. | | |
| 13 | MediCalc App. | | |
| 14 | www.siditalia.it | Società Italiana di Diabetologia (SID) | Italy |
| 15 | www.freseniuskidneycare.com | Fresenius Kidney Care | USA |
| 16 | Unicagestao.com.br | | Brazil |
| 17 | Mesogeios.gr | Mesogeios (Dialysis Center) | Greece |
| 18 | www.evidencio.com | Evidencio Medical Decision Support | Netherlands |
| 19 | Evidencio® App. | | |
| 20 | Centroestudosemilioribas.org.br | CENTRO DE ESTUDOS EMÍLIO RIBAS | Brazil |
| 21 | Leblogmedical.fr | Le Blog Medical | France |
| 22 | Easycalculation.com (English Version) | Easycalculation.com | India |
| 23 | Nephromatic.com | Nephromatic.com | NA[a] |
| 24 | clairance-creatinine.fr | clairance-creatinine.fr | France |
| 25 | Medicalcul.free.fr | Medicalcul.free.fr | France |
| 26 | Medicalcul App. | | |
| 27 | 360medics.com | 360Medics | France |
| 28 | tinkershop.net | tinkershop.net | NA[a] |
| 29 | Endmemo.com | Endmemo | NA[a] |
| 30 | Medical Calculator App. | IOBear | Taiwan |
| 31 | Dialysis Calculator App. | Rodrigo Sepulveda Palamara | Chile |
| 32 | eGFR Calculator App. | Reda Brahimi | NA[a] |
| 33 | GFR Calculator App. | medsoftpro.ru | Russia |
| 34 | Medical Calculator (WebClinicCal) App. | WebClinic (Urrutikoetxea) | Spain |
| 35 | eGFR Calc App. | Med-Mobile.eu | NA[a] |
| 36 | eGFR Calculator App. | Blue Rock | NA[a] |
| 37 | Mosa: GFR (TFG Calculator) App. | Reinaldo Mojica Acros | NA[a] |
| 38 | Калькулятор СКф App. | DLS Unity | Russia |
| 39 | eGFR (Scr/Scys) App. | DLS Unity | |
| 40 | GFR Calculator (Kidney Health) App. | Intelligent Solutions | Pakistan |
| 41 | Neph+ App. | Tricida Inc. | USA |
| 42 | Xiga eGFR Calculator App. | Virtual Software House | NA[a] |
| 43 | Doc Calculator App. | Skhelp | India |
| 44 | DNMS (Diabetic Nephropathy Management Support) App. | Dr CP Ho | Hong Kong |
| 45 | Filtracion Glomerular App. | Carrere Diseno & Ingenieria | Argentina |
| 46 | Medical Calculator App. | Explore Book | India |
| 47 | RenalExact App. | Moneer | NA[a] |

[a]NA = Not available/Not Mentioned. Last accessed on 2022 July 10.

## DISCUSSION

The eGFR calculation is important for patients, clinicians, and laboratory personnel. The CKD-EPI equation is the most recommended one internationally, but when this equation is inapplicable (like in countries that didn't standardize the creatinine methods among their laboratories), the MDRD will be a suitable choice. The decision about the correct version of the MDRD equation is depending on laboratory information. The laboratory personnel is responsible for supplying information about the creatinine method used and if it is IDMS traceable or not. On the other side, we have the developer person/team who builds this equation on a website or mobile application platform.

Following are the general comments we have found during our search for the MDRD equation:

1. Few builders didn't differentiate between the two equations (simplified and updated MDRD),
2. Several builders didn't mention the importance of IDMS traceability and its effect on MDRD equation,
3. On the other hand, many builders have this knowledge and offered it clearly in a simple way.

The following are a few real examples of the errors that may few builders do unintentionally:

1. QxMD is a well-known organization that has a famous website and a mobile application (QxCalculate with more than 1 million downloads), but they are using the simplified MDRD value (Table 5 – No. 1 and 2). It would be better if they updated the equation, to the IDMS updated MDRD.

2. Medscape® is a reputed medical website and it is using the QxMD's software (Table 5 – No. 3 and 4) in the website and mobile application (with more than 5 million downloads), which means the error has been copied here. Also, there is a Brazilian website that linked its MDRD calculation with Medscape's page (Table 5 – No. 20).
3. Several websites (16% of our sample) have expressed the eGFR value using the wrong unit (ml/min) instead of (ml/min/1.73 $m^2$), which is not accurate as all versions of MDRD have been adjusted for the standard body surface area (1.73 $m^2$). But in special cases; where ml/min unit is needed, like for drug dosing adjustment in very large or small patients, then we need to remove the adjustment [18], however, the value will be different.
4. Few websites give unexplained values which are far from the MDRD's value, for example, calculators in Table 5: Nos. 31, 38, and 39, or when you choose the mg/dL unit for creatinine like calculators in table 3, No. 6, table 4 No. 19, and table 5 No. 21.
5. In rare cases there are websites with multiple languages, they used the updated MDRD equation in all languages except English where they used the simplified MDRD (Table 5: No. 22).
6. Also sometimes the same developer has created two websites or/and applications, and both give different values (example 1: Table 4: No. 36 and Table 5: No. 31, example 2: Table 4: No. 21 and Table 5: No. 27).

There is a new challenge raised recently in 2021, as many international guidelines/organizations have removed the black race factor in the CKD-EPI equation [30, 36, 37]. But we are still waiting for the other bodies to state their recommendations. Regarding the MDRD equation, there is no consensus on removing the race factor for it as it is for CKD-EPI, hence we advocate omitting it for MDRD calculation.

## CONCLUSION

MDRD equation is still adopted and routinely used internationally in many countries, so we need to be aware of all related information that may affect its role in clinical practice.

The creatinine standardization program is unclear to many practitioners from multiple clinical fields, besides, it is not adopted in many countries around the world; so this will affect the method we are using in the calculation. Also, clinical laboratories from all over the world are encouraged to use IDMS traceable creatinine methods, as this will further help in the harmonization of eGFR reporting.

Good communication between clinical and laboratory staff is important to improve patient safety and the MDRD equation is a good example of the real need for this kind of cooperation, which reflects in the more accurate result and better patient management.

Our recommendations to the developers of the MDRD equation (including the Laboratory Informative Systems - LIS developers):

It is preferred to follow the NIDDK recommendations to the Software Vendors by adopting the IDMS-traceable MDRD equation [19], and also take into account the developing countries that didn't start yet creatinine standardization program. So, depending on that, we are suggesting the following tips:

1. The better scenario is to offer both values of simplified and updated MDRD (table 3), with a clear explanation of the different values of both equations (IDMS and non-IDMS methods).
2. It is a good option to go with the updated MDRD value only (Table 4), but also, we need to mention the importance of using the updated version and its relation with the creatinine standardization program.
3. Don't build any equation depending on simplified MDRD alone (Table 5), as the majority of creatinine methods now are standardized.
4. Use only the correct unit to express the values (ml/min/1.73 $m^2$).
5. If you want to create the equation in multiple languages, use the same equation and criteria.

Our recommendations to any user searching for MDRD:

1. Most updated guidelines recommend using CKD-EPI not MDRD for many reasons (mentioned earlier), so if any updates are involving CKD-EPI specifically (for example removing the black race factor), then it is wise to check the CKD-EPI value instead, or in parallel with MDRD.
2. Use the trusted international resources (like NIDDK…etc.), or choose the equations that mention the IDMS traceability concept.
3. For the clinical physicians, consider connecting with the clinical laboratory to check for the IDMS traceability of the creatinine reagent.

The future survival of the MDRD equation among other developed eGFR equations is related to several factors; first is the application of creatinine standardization program in developing countries, and second is including the MDRD equation in the current and future clinical studies e.g. pharmacokinetic studies on drug dosing in patients with impaired renal functions.

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