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Ethnic Prevalence of Angiotensin-Converting Enzyme Deletion (D) Polymorphism and COVID-19 Risk: Rationale for Use of Angiotensin-Converting Enzyme Inhibitors/ Angiotensin Receptor Blockers

血管緊張素I轉化酶缺失(D)的種族患病率多態性與COVID-19風險: 血管緊張素I轉化酶抑制劑/血管緊張素受體阻滯劑使用原理闡述

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Abstract 摘要

Rationale 原理闡述

Hypertension, obesity and diabetes are major risk factors associated with morbidities underlying COVID-19 infections. Regression analysis correlated presence of ACE insertion/ deletion (I/D) polymorphism to COVID-19 incidence and mortality. Furthermore, COVID-19 prevalence correlated to allele frequency of angiotensin-converting enzyme (ACE) deletion (D) polymorphism within the European population.

高血壓、肥胖和糖尿病是潛在COVID-19感染相關的主要危險因素。血管緊張素轉換酶(ACE)插入/缺失(I/D)多態性與COVID-19發病率和死亡率的相關性回歸分析。此外，在歐洲人群中，COVID-19的流行與血管緊張素I轉化酶(ACE)缺失(D)多態性的等位基因頻率有關。

Objective 目的

Homozygous ACE deletion polymorphism is associated with increase in ACE and angiotensin II (Ang-II), sustained levels can result in inflammation, fibrosis and organ damage. The ACE DD polymorphism is also associated with hypertension, acute respiratory distress and diabetic nephropathy, all considered high risk for COVID-19 infection and outcomes. The study objective was to describe a biological framework associating ethnic prevalence of ACE deletion polymorphism to COVID-19 comorbidities providing rationale for therapeutic utility of ACE-I/ ARBSs to improve outcomes.

純合ACE 缺失多態性與血管緊張素轉換酶和血管緊張素 II (Ang-II，下文用Ang-II替代)的增加相關，持續的高水準可導致炎症、纖維化和器官損傷。ACE DD 基因多態性還與高血壓、急性呼吸窘迫和糖尿病腎病有關，這些疾病都被認為是COVID-19疾病感染和預後的高危因素。這項研究的目的是描述一個生物學框架，就是將 ACE 缺失多態性的種族患病率與COVID-19合併症相聯系，為ACE-I/ARBSs 的治療效果改善預後提供理論依據。

Method and Results 方法和結果

The Allele Frequency Database (ALFRED) was queried for frequency of rs4646994 representing ACE I/D polymorphism. In a total of 349 worldwide population samples, frequency of ACE D allele was higher in European, Asian, and Africans cohorts. In the USA, the frequency of ACE D allele was higher in non-Hispanic Black compared with non-Hispanic White and Mexican Americans.

等位基因頻率資料庫(ALFRED)中查詢表示ACE I/D多態性的rs4646994的頻率。在來自全球349個人口樣本中，ACE D等位基因的頻率在歐洲、亞洲和非洲人群中較高。在美國，ACE D等位基因在非西班牙裔黑人中出現的頻率高於非西班牙裔白人和墨西哥裔美國人。

Conclusion 結論

COVID-19 binding mediated reduction/inactivation of ACE-II can increase ACE/Ang-II signalling pathway and related pathologies. The presence of ACE DD polymorphism with COVID-19 infection likely augments ACE/Ang-II activities, increasing severity of COVID-19 morbidities and impacts outcomes. Thus, ethnic prevalence of ACE DD polymorphism can explain in part the severity of COVID-19 morbidity providing rationale for the use of ACE-I/ARBSs to improve outcomes.

COVID-19結合介導的 ACE-II 減少/失活可增加 ACE/Ang-II 信號通路及相關病理。在COVID-19感染中存在ACE DD多態性可能增強ACE/Ang-II活性，增加COVID-19疾病的嚴重程度並影響預後。因此，ACE DD多態性的種族患病率可以部分解釋COVID-19發病的嚴重程度，為使用ACE- I/ARBSs改善預後提供依據。

Introduction 引言

The SARS-CoV-19 (COVID-19) infection has infected in excess of seventeen million individuals around the globe and is designated as a pandemic by the World Health Organization. The global efforts are focused on understanding the disease onset, progression and to identify causal linkage for differences in observed outcomes among the affected population and within specific demographics. Despite worldwide spread of the COVID-19 infections, European countries and the USA appear to have experienced higher incidence and mortality rates [1,2,3]. Hypertension, obesity, and diabetes were identified as the most common comorbidities associated with COVID-19 infection; higher severity of disease and mortality was generally reported in the elderly (>50 years) population.

SARS-CoV-19 (COVID-19)感染了全球1700多萬人，被世界衛生組織定為全球流行病。全球努力的重點是瞭解疾病的發病、進展，並確定受影響人口之間和特定人口統計數據中觀察到的結果差異的因果聯繫。儘管COVID-19傳染病在全球範圍蔓延，但歐洲國家和美國的發病率和死亡率似乎較高[1,2,3]。高血壓、肥胖和糖尿病被確定為與COVID-19感染相關最普遍合併症;老年人(> 50歲)的疾病嚴重程度和死亡率普遍較高。

Angiotensin-converting enzyme 2 (ACE2) is the predominant receptor for SARS-CoV viral entry and infection, resulting in the reduction of expression of ACE2 [4, 5]. ACE2 is an enzyme component of the renin-angiotensin system (RAS), a complex integrated network of peptides-enzyme combination, generating catalytically active peptides with prominent influence on the vascular, renal, cardiac, and immune system [6]. In this report, we describe a framework of the pathophysiological consequence of COVID-19-induced reduction in ACE2, i.e., overactivation of the RAS pathway with the potential to have deleterious effect on organ functions including the lungs, kidneys, heart, and immune system. The deleterious activities of RAS within the COVID-19-infected cohorts can be further amplified by the presence of genetic polymorphism in the angiotensin-converting enzyme (ACE). Increased prevalence in frequency of the ACE polymorphism within ethnic groups, in part, is likely responsible for the observed severity of COVID-19 comorbidities and mortality in this population. This is substantiated by recent regression analysis linking presence of ACE-1 I/D (insertion/deletion) polymorphism with incidence and mortality with COVID-19 infection [7].

血管緊張素轉化酶2（ACE2）是 SARS-CoV 病毒進入和感染的主要受體，這導致 ACE2 [4, 5]的表達減少。血管緊張素轉換酶2是腎素-血管緊張素系統（RAS，下文均用RAS替代）的一個酶組分，該系統是一個由多肽-酶組合而成的複雜綜合網路，能產生具有催化活性的多肽，從而對血管、腎臟、心臟和免疫系統產生顯著影響[6]。在本報告中，我們描述了 COVID-19誘導 ACE2減少的病理生理學結果的框架，即過度啟動 RAS 通路，可能對器官功能包括肺、腎臟、心臟和免疫系統產生有害影響。在 COVID-19感染的同源群體中 RAS 的有害活性可以通過血管緊張素轉化酶(ACE)基因的遺傳多態性進一步放大。種族群體中 ACE 多態性頻率的增加，在某種程度上可能是該人群中觀察到的嚴重的COVID-19疾病合併症和死亡率的原因。最近美國回歸分析學會將 ACE-1 I/D (插入/缺失)多態性的存在與COVID-19疾病感染的發病率和死亡率聯繫起來，證實了這一點[7]。

Renin-Angiotensin System: ACE, Ang-II, and Inflammation

腎素-血管緊張素系統（RAS): 血管緊張素轉化酶，血管緊張素-2(下文均用Ang-II替代），和炎症

The RAS system has a prominent role in the regulation of vascular dynamics; its components directly or indirectly influence functions of the lung, heart, kidney, brain and the immune system [6]. In addition to central RAS components, i.e., renin (kidney), ACE (lungs), and angiotensinogen (liver), tissue-specific localized systems including the kidney, heart, and lungs have been identified [6, 8]. Within RAS, the canonical angiotensin-converting enzyme (ACE) is responsible for conversion of angiotensin-1 (Ang-I) to angiotensin-2 (Ang-II) (Fig. 1a). Subsequently, Ang-II mediates its effects through activation of AT-1 and AT-2 receptors, resulting in distinct intracellular signalling pathways [9,10,11]. Activation of AT-1 receptors is associated with the well-characterized physiological actions of Ang-II in various organs including the lung, heart, kidney, and the vascular system [10].

RAS 系統在調節血管動力學方面有重要作用，其組成部分直接或間接地影響肺、心臟、腎臟、大腦和免疫系統的功能[6]。除了腎素(腎)、血管緊張素原(肺)和血管緊張素原(肝)等中樞 RAS 成分外，還發現了包括腎、心臟和肺在內的組織特異性局部系統[6, 8]。在 RAS 系統中，典型的血管緊張素轉化酶(ACE)負責血管緊張素-1(Ang-I)轉化為血管緊張素-2(Ang-II)(圖1a)。隨後，Ang-II 通過

啟動 AT-1和 AT-2受體介導其作用，導致不同的細胞內信號通路[9,10,11]。AT-1受體的啟動與 血管緊張素-2(Ang-II)在包括肺、心臟、腎臟和血管系統在內的各種器官中的生理作用有關[10]。

Fig. 1 (Full size image)

圖一 （下載原尺寸圖片）

a Overview of the renin-angiotensin system. The figure describes the basic components of the renin angiotensin system with focus on the impact of ACE and ACE2 in the generation of angiotensin peptides, the respective cognate receptor(s) and corresponding physiological consequence of receptor activation. **b** Influence of ACE deletion (DD) polymorphism on renin-angiotensin system. The figure describes the consequence of the ACE deletion polymorphism, the increase in levels of ACE and angiotensin II resulting in activation of AT-1 receptor and downstream pathophysiological effects. **c** Consequence of COVID-19 infection and ACE Deletion (DD) polymorphism on renin-angiotensin system. The figure describes the increased activation of ACE and generation of Ang-II as a consequence of COVID-19-mediated reduction in ACE2 in the presence of ACE deletion polymorphism. The result is disruption of physiological balance of the ACE/ACE2 axis resulting in overactivation of AT1-R signalling and associated pathological consequence

a. RAS系統概述。該圖描述了RAS的基本組成，重點介紹了 ACE 和 ACE2在血管緊張素肽生成中的作用、各自的同源受體及受體啟動的相應生理後果。b. ACE 缺失(DD)多態性對RAS。該圖描述了 ACE 缺失多態性的後果，ACE 和**Ang-II** 水準的增加導致 AT-1受體的啟動和下游病理生理效應。c. COVID-19疾病感染和 ACE 基因多態性對RAS的影響。該圖描述了 ACE 啟動增加和**Ang-II**的產生是由於存在 ACE 缺失多態性 covid-19介導的 ACE2減少。其結果是 ACE/ACE2軸的生理平衡被破壞，導致 AT1-R 信號的過度啟動和相關的病理後果

Full size image 下載原尺寸圖片

In addition to its hemodynamic effect, Ang-II has significant pro-inflammatory effects, promoting generation of reactive oxygen species (ROS), cell proliferation, extracellular matrix remodelling, and regulation of gene expression via signalling pathways leading to tissue injury [8, 12]. Ang-II promotes expression of pro-inflammatory chemokines in the kidneys, heart, and vasculature to induce inflammation [13]. Several studies have characterized key inflammatory processes influenced by Ang-II on macrophages, dendritic cells, and mesangial cells resulting in mobilization and activation of cytokines, chemokines, and pro-inflammatory factors resulting in tissue damage and progressive organ failure [14]. Due to profound influence of Ang-II signalling pathways that are predominantly adverse when unmitigated, the potency of Ang-II is tightly regulated via proteolytic activities of enzymes to generate various angiotensin peptide fragments with physiological activities different from Ang-II [14] (Fig. 1a). ACE2 is an enzyme component of RAS, with proteolytic activities different from the canonical ACE. ACE2 is responsible for cleaving angiotensin I to Ang (1–9) and angiotensin-2 to Ang (1–7) peptides respectively (Fig. 1), of which the latter is a potent vasodilator [15, 16]. Several studies support a major role for Ang (1–7) in providing the counterbalance to the physiological effects of Ang-II [17,18,19]. Thus, the pro-inflammatory effects of ACE/Ang-II axis are balanced by activation of anti-inflammatory pathways by ACE2 and other systems.

除了血液動力學作用，Ang-II還具有顯著的促炎症作用，促進活性氧（ROS）的產生，細胞增殖，細胞外間質重塑，以及通過信號通路調節基因表達導致組織損傷[8,12]。Ang-II促進炎症趨化因

數在腎臟、心臟和血管系統的表達以誘導炎症[13]。一些研究表明，Ang-II 影響巨噬細胞、樹突狀細胞和系膜細胞的關鍵炎症過程，導致細胞因數、趨化因數和促炎因數的動員和啟動，從而導致組織損傷和進行性器官衰竭[14]。由於Ang-II信號轉導途徑的深刻影響，這些途徑主要是逆轉的，所以Ang-II的效力是通過酶的蛋白水解活性來產生各種血管緊張素肽片段，其生理活性不同於Ang-II[14](圖1a)。ACE2是 RAS 的一個酶組分，具有不同於正規 ACE 的蛋白水解活性。ACE2分別參與血管緊張素-I (angiotensin I，Ang)(1-9)和血管緊張素-II(angiotensin-II，Ang)(1-7)的分離(圖1)，其中血管緊張素2是一種強有力的血管擴張劑[15,16]。一些研究支援血管緊張素(1-7)在提供抗衡Ang-II [17,18,19]的生理效應的主要作用。因此，ACE/Ang-II 軸的促炎作用是通過 ACE2和其他系統啟動抗炎通路來平衡的。

ACE Insertion/Deletion (ID) Polymorphisms: Prevalence ACE 基因插入/缺失(ID)多態性: 患病率

Two recent publications reported that ACE insertion/deletion polymorphism correlated to infectivity and mortality associated with COVID-19 infections [7, 20]. In humans, the gene encoding ACE is located on chromosome 17 and exhibits an insertion/deletion polymorphism that is characterized by an insertion (allele I) or deletion (allele D) of a 287 base pair marker in intron 16 that results in three different genotypes, i.e. DD or II homozygotes or ID heterozygotes. It is reported that the deletion (D) allele occurs in 55% of the population and associated with increased ACE activity, implicating the presence of D allele with disease pathologies associated with RAS activity [21].

兩個最近的出版物報導 ACE 插入/缺失多態性與COVID-19疾病感染的傳染性和死亡率相關[7, 20]。在人類中，編碼 ACE 的基因位於17號染色體，具有插入/缺失多態性，即內含子16中一個287個堿基對標記的插入/缺失(等位基因I)或擁有屬性(等位元基因 D)，導致產生3種不同的基因型，即 DD 或 II 純合子或 ID 雜合子。據報導，缺失(D)等位基因發生在55% 的人口和增加 ACE 活性，提示 d 等位基因的存在與 RAS 活性相關的疾病病理[21]。

The Allele Frequency Database (ALFRED; https://alfred.med.yale.edu/alfred/index.asp; RRID:SCR_001730) was queried for frequency of rs4646994 representing ACE I/D polymorphism, one of the best studies of all ACE polymorphisms. The allelic frequencies of the insertion (I, +) and deletion (D, –) genotypes within various geographic regions from 349 population samples were obtained from ALFRED and are summarized in Table 1. Inclusion of data from all European studies demonstrated almost equal distribution of the ACE (I) or ACE (D) allele, with Italians, Ashkenazi Jews and Canarians demonstrating slightly higher prevalence compared with the population averages. In contrast to Europe, among the African population, the frequency of D allele was almost twice compared with the I allele among 2126 population samples with highest levels observed in Pygmies, Ethiopian Jews, Moroccan, Nigerian and Tunisian populations. These are consistent with other studies reporting significant increase in the frequency of deletion polymorphism of ACE observed in individuals of African descent and associated with disease pathology [22]. Specifically, a prevalence of the D allele of 60% has been reported in individuals of African descent [22]. In the USA, the non-Hispanic Black population has higher frequency of the D allele (Table 2) compared with non-Hispanic White and Mexican American population [23]. The frequency of the D allele was increased compared with the I allele within the Middle Eastern population with higher values observed in both Arab and Saudi Arabia sample populations. In contrast to Africa and Middle East, increased

frequency of the I allele was observed in sample populations from Asia (India, Pakistan Nepalese, Tajik regions and Sri Lanka), Oceania (New Zealand, Papua New Guinea and Micronesia), East Asia (China, Japan, Korea, Taiwan, Cambodia, Vietnam, Philippines and Malaysia) and South American countries.

等位元基因頻率資料庫(ALFRED; https://ALFRED.med.yale.edu/ALFRED/index.asp ; RRID: SCR _ 001730)查詢了 rs4646994代表 ACE I/D 多態性的頻率，這是所有 ACE 多態性研究中最好的一個。從349個群體樣本中獲得了插入(I，+)和缺失(D，-)基因型在不同地理區域的等位元基因頻率，總結見表1。納入所有歐洲研究的資料表明，ACE (I)或 ACE (D)等位基因的分佈幾乎相等，義大利人、德系猶太人和卡納裏亞印第安人的患病率略高於人口平均水準。在2126個人口樣本中，D 等位元基因的頻率幾乎是 I 等位元基因頻率的兩倍，在俾格米人、衣索比亞猶太人、摩洛哥人、奈及利亞人和突尼斯人中觀察到的 D 等位元基因頻率最高。這些結果與其他研究報告的結果一致，即在非洲人後裔個體中觀察到的 ACE 基因缺失多態性的頻率顯著增加，並與疾病病理學有關[22]。具體而言，在非洲人後裔中，D 等位基因的患病率率為60% [22]。在美國，非西班牙裔黑人人口有更高的 D等位元基因頻率(表2)相比，非西班牙裔白人和墨西哥裔美國人口[23]。D 等位元基因頻率在中東人群中比I等位元基因頻率增加，在阿拉伯和沙烏地阿拉伯樣本人群中觀察到的數值更高。與非洲和中東不同，在亞洲(印度、巴基斯坦尼泊爾、塔吉克地區和斯里蘭卡)、大洋洲(紐西蘭、東南亞和密克羅尼西亞)、東亞(中國、日本、韓國、臺灣、柬埔寨、越南、菲律賓和馬來西亞)和南美國家的樣本人群中觀察到 I等位元基因頻率增加。

Table 1 Prevalence of ACE insertion/deletion polymorphism: the Allele Frequency Database (ALFRED) was queried for identifying population frequency of the ACE insertion/deletion polymorphism among geographical locations. From a total of 349 population samples, the average frequencies of the insertion and deletion allele for ACE were calculated for the different geographical locations. The table provides the population sample size and frequency (italicized) and the breakdown of the frequency of the insertion and deletion allele within specific ethnic groups of interest within the population

表1 ACE 插入/缺失多態性的普遍性: 為了確定不同地理位置間 ACE 插入/缺失多態性的人群頻率，我們對等位元基因頻率資料庫(Allele Frequency Database, ALFRED)進行了查詢。從349個人群樣本中，計算了 ACE 基因插入和缺失等位基因在不同地理位置的平均頻率。該表提供了人口抽樣數量和頻率(斜體) ，以及人口中特定種族群體內插入和刪除等位元基因頻率的細目

Full size table 下載全尺寸表格

		樣本大小 (*N*)	插入	缺失
歐洲		*16,220*	*0.412*	*0.588*

		樣本大小 (*N*)	插入	缺失
	阿巴齊安人	24	0.000	1.000
	加納裏安	1358	0.375	0.625
	英國人	924	0.454	0.546
	法國人	2234	0.423	0.578
	愛爾蘭人	226	0.429	0.571
	義大利人	222	0.342	0.658
	猶太人, 阿什凱納齊	154	0.340	0.660
非洲		*2126*	*0.340*	*0.660*
	俾格米人	68	0.221	0.779
	猶太人, 埃塞俄比亞	64	0.203	0.797
	摩洛哥人	106	0.292	0.708
	尼日利亞人	22	0.273	0.727
	突尼斯人	200	0.325	0.675
中東		*1714*	*0.360*	*0.640*
	阿拉伯人	100	0.290	0.710
	沙特人	540	0.275	0.725
亞洲		*7380*	*0.585*	*0.414*
大洋洲		*1444*	*0.684*	*0.315*
東亞		*3182*	*0.627*	*0.372*
南美		*2458*	*0.706*	*0.293*

Table 2 ACE polymorphism allele and genotype frequencies: the prevalence of 289-bp Alu insertion/deletion in intron 16 of ACE gene corresponding to rs4646994 within the non-Hispanic White and non-Hispanic Black population is described. (Information modified from source provided by Office of Science (OS), Office of Genomics and Precision Public Health, CDC 2009; complete data is available at https://www.cdc.gov/genomics/population/genvar/frequencies/ace.htm)

表2 ACE 多態性等位元基因和基因型頻率: 在非西班牙裔白人和非西班牙裔黑人人口中，ACE 基因內含子16中與 rs4646994相對應的289-bp Alu 插入/缺失的流行率被描述。(資訊修改自2009年疾病預防控制中心基因組學與精確公共衛生辦公室科學辦公室(OS)提供; 完整資料查詢網址 https://www.cdc.gov/genomics/population/genvar/frequencies/ace.htm)

Full size table 下載全尺寸表格

基因變異	民族/種族	等位基因%		等位基因% (95% 置信區間)			卡方檢驗p值	HW *p* 值
		D	I	DD	DI	II		
rs4646994	非-西班牙裔 白人	54.6	45.4	28.8 (25.9,31.8)	51.6 (47.8,55.3)	19.6 (17.7, 21.8)	< 0.001	0.11
	非-西班牙裔 黑人	58.7	41.3	33.8 (31.5,36.3)	49.8 (47.3,52.2)	16.4 (14.6,18.5)		0.1

ACE Deletion (D) Polymorphism and Disease—Increased Susceptibility and Severity to Co-morbidities Associated with COVID-19

ACE 缺失(D)基因多態性與疾病—與COVID-19疾病相關的合併症易感性和嚴重程度增加

Although the ACE I/D polymorphism is located in a non-coding region, its presence is directly linked to regulation of renin-angiotensin system and associated pathological conditions. A positive association between D allele and high blood pressure, atherosclerosis, coronary artery disease, stroke, diabetic nephropathy and Alzheimer's disease has been extensively reviewed [24]. The molecular underpinning of these diseases is multi-factorial and complex, and the presence of the ACE deletion polymorphism may contribute to influence disease pathology. Indeed, to date, there is distinct lack of consensus studies linking the presence of ACE deletion polymorphism to disease causality. Nevertheless, the increase in levels of ACE in individuals with the ID and DD genotypes and potential augmentation of the RAS system and associated signalling cascades can influence pathways to influence disease pathology [25] (Fig. 1b). Indeed, increased levels of ACE and Ang-II have been implicated in the pathophysiology of lung (pulmonary hypertension, pulmonary fibrosis, acute lung injury and acute respiratory distress syndrome [26, 27]) and kidney disease (chronic kidney disease, diabetic nephropathy [28, 29]). In the African American population, the deletion polymorphism is associated with increase in systolic blood pressure, hypertension and altered vascular reactivity with potential impact on cardiovascular disease [30,31,32].

儘管 ACE I/D 多態位於非編碼區，但它的存在與RAS和相關病理狀態的調節直接相關。D 等位基因與高血壓、動脈粥樣硬化、冠狀動脈疾病、中風、糖尿病腎病和阿爾茨海默氏病之間的正相關已經得到廣泛的研究[24]。這些疾病的分子基礎是多因素和複雜的，ACE 缺失多態性的存在可能有助於影響疾病的病理。事實上，到目前為止，明顯缺乏共識的研究，將 ACE 缺失多態性的存在與疾病的因果關係聯繫起來。儘管如此，在 ID 和 DD 基因型個體中 ACE 水準的增加和 RAS 系統

的潛在增強以及相關的信號通路可以影響疾病病理學的通路[25] (圖 1b)。事實上，ACE 和 Ang-II 水準的升高與肺部病理生理學(肺部高壓、肺纖維化、急性肺損傷和急性呼吸窘迫症候群[26, 27])和腎臟疾病(慢性腎臟疾病、糖尿病腎病疾病[28, 29])有關。在非洲裔美國人中，缺失多態性與收縮壓升高、高血壓和血管反應性改變有關，對心血管疾病有潛在影響[30,31,32]。

A subset of individuals with a positive diagnosis of COVID-19 infection have rapid progression of lung dysfunction leading to acute respiratory distress with potential need for ventilatory support [2, 3]. Presence of ACE insertion/deletion (I/D) polymorphism is associated with susceptibility and is an independent risk factor for mortality in patients with acute respiratory distress syndrome (ARDS) [33, 34]. Of the three ACE polymorphisms, there is positive association with frequency of the DD allele and incidence of ARDS, increased fatality and a prognostic factor of outcomes [35,36,37]. Further, the DD genotype is usually associated with higher ACE levels relative to other genotypes and with increased mortality in acute lung injury (ALI)/ARDS patients [38, 39]. Elevated levels of ACE have been observed in the bronchoalveolar fluid of individuals with ARDS [28]. Although decreases in circulating ACE have been reported in ARDS patients [40], this might be a consequence of the progressive damage to lung tissue as increased levels of ACE are evident in the bronchoalveolar fluids of individual with ARDS [40]. The positive relationship between DD genotype and ALI/ARDS and the corresponding increase in ACE levels suggest the potential involvement of increased Ang-II in the etiopathology of ARDS. During the avian (H7N9) flu infections, approximately 70% of patients developed ARDS [41]. In a subset of infected patients, increase in plasma Ang-II levels was linked to severity and fatal outcomes [41].

一組確診為COVID-19感染的患者肺部功能障礙進展迅速，導致急性呼吸窘迫，可能需要呼吸支持[2, 3]。ACE 插入/缺失(I/D)多態性的存在與急性呼吸窘迫症候群易感性有關，是導致急性呼吸道窘迫綜合症（ARDS，下文用ARDS替代）患者死亡的獨立危險因素。[33, 34].在三個 ACE 基因多態性中，DD 等位元基因頻率與 ARDS 發生率、病死率和預後因素呈正相關[35,36,37]。此外，DD 基因型通常與其他基因型相對較高的 ACE 水準有關，並且與急性肺損傷(ALI)/ARDS 患者死亡率增加有關[38, 39]。在 ARDS 患者的支氣管肺泡液中觀察到 ACE 水準升高[28]。雖然在 ARDS 患者中已有迴圈 ACE 下降的報導[40],，但這可能是由於 ARDS 患者的支氣管肺泡液中 ACE 水準明顯升高導致肺組織進行性損害的結果[40]。DD 基因型與 ALI/ARDS 呈正相關，ACE 水準相應升高，提示 Ang-II 水準升高可能參與 ARDS 的發病機制。在禽流感(H7N9)感染期間，大約70% 的患者出現了 ARDS。在一部分感染患者中，血漿 Ang-II 水準的升高與嚴重程度和致命後果有關[41]。

Within the COVID-19-infected population, there is increased incidence of kidney injury associated with higher mortality rates [42, 43]. Chronic kidney disease (CKD) is associated with severity of COVID-19 infection [44]. Interestingly, both ACE and ACE2 expressions in the kidneys are predominant in the proximal tubules with minor expression in the glomerular apparatus [45]. The balance between Ang-II and Ang (1–7) affects renal RAS to maintain balance of kidney functions; imbalance of the ratio results in kidney disease [46,47,48]. Chronic kidney disease is characterized by decreases in cardiac and renal ACE2 in human [49]. Diabetic nephropathy (a CKD) is characterized by decrease in ACE2, increased ACE and Ang-II-mediated tubular and glomerular damage as a result of renal RAS activation [28, 29]. Based on these studies, the ability of COVID-19 to bind and decrease ACE2 in target tissues is most likely responsible for the observed increase in blood urea nitrogen, proteinuria and hematuria associated with kidney damage [49]. Thus, COVID-19-associated decrease in ACE2 most likely results in disruption of the ACE/ACE2 balance in the kidney leading to sustained activation of ACE and Ang-II

activities and kidney damage. ACE insertion/deletion polymorphism is also associated with diabetic kidney disease, the frequency of DD and ID genotype distribution being higher compared with non-diabetic kidney disease cohorts, leading to functional decline [50, 51]. The above observations suggest that presence of the DD genotype of ACE in patients with COVID-19 infection may be associated with severe respiratory distress compared with the other genotypes.

在COVID-19感染人群中，與較高死亡率相關的腎損傷發生率增加[42, 43]。慢性腎臟疾病(CKD)與COVID-19疾病感染的嚴重程度相關。有趣的是，ACE 和 ACE2在腎臟中的表達在近端腎小管中占主導地位，而在腎小球器官中的表達較少[45]。Ang-II和Ang(1-7)之間的平衡影響腎臟 RAS 以維持腎臟功能的平衡，比例導致腎臟疾病[46,47,48]。慢性腎病以人的心腎ACE2下降為特徵[49]。糖尿病腎病(CKD)的特點是ACE2減少，ACE和Ang-II介導的腎小管和腎小球損傷增加，這是腎臟RAS啟動的結果[28, 29]。基於這些研究，COVID-19結合和降低靶組織中ACE2的能力很可能是導致血尿素氮、蛋白尿和血尿升高並伴有腎損傷的原因[49]。因此，與 covid-19相關的 ACE2減少最有可能導致腎臟中 ACE/ACE2平衡的破壞，從而導致 ACE 和 Ang-II 活性的持續啟動和腎臟損傷。ACE 插入/缺失多態性也與糖尿病腎病相關，DD 和 ID 基因型分佈頻率高於非糖尿病腎病組，導致功能下降[50, 51]。上述觀察表明，與其他基因型相比，COVID-19疾病感染患者中存在 DD 型 ACE 可能與嚴重的呼吸窘迫有關。

Multiple studies have reported on the prevalence of ACE I/D polymorphism, specifically the ID and DD polymorphism in increasing levels of ACE and Ang-II, which could in part influence susceptibility to underlying pathologies considered high risk for COVID-19 infections, progressive organ dysfunction and poor outcomes. Thus, presence of ID and DD polymorphism by itself is a potential underlying risk factor associated with severity and outcomes in individuals with positive diagnosis of COVID-19 infection [20, 21].

多項研究已報導 ACE I/D 多態性的流行，特別是在 ACE 和 Ang-II 水準增加中的 ID 和 DD 多態性，這可能一定程度上影響潛在疾病的易感性，這些疾病被認為是COVID-19疾病感染、進行性器官功能障礙和不良結果的高危因素。因此，在COVID-19陽性診斷患者中，ID和DD多態性本身就是與病情嚴重程度和預後相關的潛在潛在危險因素[20, 21]。

ACE-2 Inhibition by COVID-19: Increased RAS Activity

COVID-19抑制ACE-2: 增加 RAS 活性

The proteolytic cleavage of Ang-II by ACE2 to generate Ang (1–7) represents a major event leading to the physiological inactivation of Ang-II function. Thus, in patients with active COVID-19 infections, decrease in ACE2 expression/activity should most likely lead to sustained ACE-mediated generation of Ang-II and downstream signalling deleterious to organ functions including that of lung, kidney and heart [52]. Although the status of circulating and lung ACE levels in COVID-19 patients is unclear, the ability of SARS-CoV-2 binding specifically to ACE2 decreases its expression and activity suggesting upregulation of ACE/Ang-II-mediated activities. This is consistent with the observation that knockdown of ACE2 is associated with severe ARDS in multiple rodent models compared with corresponding wild-type controls [18]. Loss of ACE2 expression in mutant mice is associated with worse lung function and

characterized by increases in vascular permeability, lung oedema and neutrophil accumulation [18]. Interestingly, reduced plasma levels of ACE2 are also observed within populations of African descent including African Americans, specifically in individuals with pre-hypertensive status, diabetes and renal disease [53, 54]. Administration of a catalytically active recombinant ACE2 protein improved symptoms of acute lung injury in ACE2 knockout and wild-type mice [55]. In a pilot clinical investigation, administration of recombinant human ACE2 (APN311) in patients with acute respiratory distress was associated with rapid decrease in Ang-II level and did not significantly influence oxygenation indices in the treated population compared with placebo-controlled group [56]. The recombinant human ACE2 is undergoing renewed clinical testing in the COVID-19 patient population to investigate clinical outcomes [52].

血管緊張素 II(Ang-II)的蛋白水解切割產生Ang（1-7）是導致Ang-II 功能失活的一個重要事件。因此，在活性COVID-19疾病感染的患者中，ACE2表達/活性的降低很可能導致持續的ACE介導的Ang-II和下游信號通路的產生，對包括肺、腎和心臟在內的器官功能有害[52]。雖然迴圈和肺 ACE 水準在COVID-19患者中的狀況尚不清楚，但 SARS-CoV-2特異性結合 ACE2的能力降低了其表達和活性，提示 ACE/ Ang-II 介導的活性上調。這與多種齧齒動物模型與相應的野生型對照組相比，ACE2下調與嚴重 急性呼吸窘迫綜合征相關的觀察結果是一致的[18]。突變小鼠ACE2表達缺失與肺功能惡化、擁有屬性通透性增加、肺水腫和中性粒細胞積聚有關[18]。有趣的是，在包括非裔美國人在內的非洲裔人群中，特別是在高血壓前期、糖尿病和腎病患者中，血漿 ACE2水準也有所下降。給予具有催化活性的重組 ACE2蛋白可改善 ACE2基因敲除小鼠和野生型小鼠的急性肺損傷症狀[55]。在一個初步的臨床研究中，給予重組人血管緊張素轉換酶2(APN311)治療急性呼吸窘迫患者，Ang-II水準迅速下降，與安慰劑對照組相比，治療組人群的氧合指數沒有顯著影響[56]。重組人血管緊張素轉換酶2正在COVID-19疾病患者群體中重新進行臨床試驗，以研究臨床效果[52]。

ACE2 inhibition by COVID-19 Plus ACE D Polymorphism: Synergized RAS—Rationale for Use of ACE-I and ARBs in Clinical Management

COVID-19和ACE D 多態性對ACE2的抑制作用: 協同的RAS-臨床管理中使用ACE-I和ARBs的理論基礎

SARS-CoV-2 binding to ACE2 results in reduction of protein expression, activity and ability to generate anti-inflammatory signalling, all of which contribute to a pro-inflammatory phenotype due to presence of ACE activity and Ang-II signalling (Fig. 1c). Presence of ACE D polymorphism increases ACE levels and Ang-II leading to pro-inflammatory phenotype and is associated with disease susceptibilities considered high risk for COVID-19 infections. Recently, it was proposed that reduced plasma levels of ACE2 in individuals of African descent most likely lowers potential for COVID-19 infection [57]; the overall outcomes in individuals with presence of ACE deletion polymorphism after infection with COVID-19 most likely leads to exacerbation of comorbidities and overall deleterious outcomes. Based on the described biological consequence of COVID-19 infections on the RAS system, treatment with ACE-I and ARBs should be associated with improved outcomes within the overall COVID-19 patient cohorts. Indeed, several meta-analyses provide preliminary support for the potential benefits of the use of ACE-I/ARBSs in management of COVID-19 infections.

SARS-CoV-2與 ACE2結合導致蛋白質表達、活性和產生抗炎信號的能力下降，所有這些因 ACE 活性和血管緊張素轉換酶 II(Ang-II)信號的存在而促進炎症表型的產生(圖1c)。ACE D多態性的存在增加 ACE 水準和Ang-II，導致促炎症表型，並與疾病易感性被認為是COVID-19疾病感染的高風險相關。最近，有人提出，非洲血統個體血漿 ACE2水準的降低很可能降低了COVID-19疾病感染的可能性[57]; 在感染COVID-19疾病後存在 ACE 缺失多態性的個體中，總體結果最有可能導致併發症和總體有害結果的加重。基於所描述的COVID-19疾病感染對 RAS 系統的生物學後果，ACE-I和ARBs 治療應該與整個COVID-19疾病患者群體的改善結果相關聯。事實上，一些薈萃分析為使用ACE-I/ARBSs 治療COVID-19疾病感染的潛在益處提供了初步支持。

In a multicenter study of 1128 adult patients with hypertension with positive COVID-19 diagnosis, in-patient use of ACE-I/ARBS was associated with reduced risk of mortality from all causes when compared with patients not treated with the medications [58]. Recent publications further highlight the use of ACE-I and ARBs in providing cardiovascular and renal benefits to patients with COVID-19 diagnosis [59, 60]. In a meta-analysis, patients treated with ACE-I/ARBSS had 44% reduction in odds of developing severe disease and death compared with patients not treated with ACE-I/ARBSs [61]. These studies provide rationale for investigation into the utility of ACE-I/ARBSs in the ethnic population with known prevalence of ACE deletion polymorphisms in an effort to mitigate severity and improve outcomes in response to COVID-19 infections.

在一項針對1128名COVID-19陽性的成年高血壓患者的多中心研究中，與未接受藥物治療的患者相比，住院患者使用ACE-I/ARBS與各種原因的死亡風險降低有關[58]。最近的出版物進一步強調使用ACE-I和ARBs對COVID-19確診患者的心血管和腎臟有益[59, 60]。在一項薈萃分析中，接受ACE-I/ARBS治療的患者與未接受ACE-I/ARBS治療的患者相比，發生嚴重疾病和死亡的幾率降低了44% [61]。這些研究為調查ACE缺失多態性普遍存在的少數民族人群中ACE- i /ARBSs的效用，以減輕嚴重程度和改善COVID-19感染的結果提供了理論基礎。。

Use of ACE-I/ARBSs in Ethnic Population with Increased Prevalence of ACE D Polymorphism for Management of COVID-19

ACE-I/ARBs 在 ACE D基因多態性增高的少數民族人群中應用於COVID-19疾病管理

ACE is a multi-functional, relatively non-specific peptidase enzyme with a wide range of substrate specificities that impact physiological pathways in influencing blood pressure, haematopoiesis, hormone regulation, renal function and immune responses. The specificity of hypertension and cardiovascular disease as underlying causes for severity of COVID-19 infection, the inherent role of ACE-mediated generation of Ang-II and downstream signalling to potentially exacerbate inflammation and organ damage along with genotypic impact on ACE status provide compelling support of the use of ACE-I and ARBs in the clinical management of patient with positive diagnosis of COVID-19.

ACE 是一種多功能、相對非特異性的肽酶，具有多種底物特異性，在影響血壓、造血、激素調節、腎功能和免疫反應等方面影響生理途徑。高血壓和心血管疾病的特異性是COVID-19疾病感染嚴重程度的根本原因，ACE 介導的Ang-II和下游信號的內在作用可能加劇炎症和器官損傷，以

及對 ACE 狀態的基因型影響，都為在臨床上使用ACE-I和ARBs治療COVID-19陽性患者提供了有力的支持。

The biological impact of the presence of deletion polymorphism of ACE in individuals with COVID-19 infection provides a significant rationale for serious consideration of short-term use of ACE-I and/or ARBs in patients without underlying issues with blood pressure or cardiovascular disorder. The guidance statement issued by the Heart Failure Society of America (HFSA), the American College of Cardiology (ACC) and American Heart Associated (AHA) states that in the absence of favourable or detrimental effects of ACE-I and ARBs in the COVID-19 setting, the recommendation is to not arbitrarily or pre-emptively discontinue these agents in patients currently on the medication as standard of care (acc.org). Indeed, both ACE-I and ARBs have been extensively used in conditions ranging from hypertension, congestive heart failure, prevention of kidney failure and other indications. Both classes of drugs have extensive use history, understanding of safety, tolerability, efficacy, adverse events profile and drug interactions. The significant genetic, scientific and clinical data supporting a potential role for increased ACE levels and associated Ang-II effect in target organs provides compelling argument for use of ACE-I and ARBs in the clinical management of patients with COVID-19 infections to improve outcomes. High salt sensitivity–associated low plasma renin activities are responsible for the attenuated blood pressure–lowering response of ACE-I in the African American population [62]. However, this particular phenomenon might be of potential advantage in dosing and management of severity of COVID-19-associated morbidities in African American and other ethnic populations with ACE deletion polymorphism.

COVID-19感染個體中ACE缺失多態性的生物學影響，為沒有潛在血壓或心血管疾病問題的患者考慮短期使用ACE- i和/或ARBs提供了重要依據。。美國心力衰竭協會(HFSA)、美國美國心臟病學學院協會(ACC)和美國心臟協會(AHA)發佈的指導聲明指出，在COVID-19疾病環境中，如果沒有ACE-I和ARBs 的有利或不利影響，建議不要武斷或率先停止使用這些作為標準治療的藥物(acc.org)。事實上，ACE-I和ARBs都被廣泛應用於高血壓、心衰竭、預防腎功能衰竭和其他適應症。這兩類藥物都有廣泛的使用歷史，並瞭解其安全性，耐受性，療效，不良事件概況和藥物相互作用。重要的遺傳學、科學和臨床資料支援 ACE 水準升高的潛在作用以及靶器官中相關的 Ang-II 效應，為在COVID-19感染患者的臨床管理中使用ACE-I和ARBs 改善預後提供了令人信服的論據。高鹽敏感性相關的低血漿腎素活性是造成非裔美國人ACE-I 降低血壓反應減弱的原因[62]。然而，該特殊現象可能存在於非裔美國人和其他具有ACE缺失多態性的種族人群中，對COVID-19相關病症的嚴重程度的劑量和管理具有潛在優勢。

In summary, this study describes the biological relevance of genetic polymorphism of ACE deletion with higher prevalence in certain ethnic populations including African Americans in context of COVID-19 infection and rationale for the use of ACE-I/ARBSs for therapeutic management of severity of morbidity and improving outcomes associated with COVID-19.

綜上所述，本研究描述了 ACE 缺失基因多態性與某些種族人群包括非裔美國人在COVID-19疾病感染背景下較高患病率的生物學相關性，以及使用 ACE-I/ARBSs 治療疾病嚴重程度和改善與改善COVID-19相關預後的原理。

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