



# Sex and Age Differences in Telomere Length and Susceptibility to COVID-19

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## ABSTRACT

**Background:** Telomeres are the ends of a chromosome and play a fundamental role as vanguards contra the chromosomal decay. Due to the inability of DNA polymerase to replicate chromosomal ends, a reduction in telomeres length happens after each cell division. The existence of shorter telomeres in older people is related to diminish immune functions. Viral infections able to stimulate remodeling of cells, stress responses, and telomere shortening. Moreover, telomere shortening can be caused by extrinsic environmental variables which induce oxidative stress under conditions of inflammation.

**Aim:** To identify the correlation between telomere shortening and susceptibility to Novel Coronavirus Disease 2019 (COVID-19). In addition to clarifying changes in telomere length according to the viral infection, the effect of sex and age differences in telomere length in confirmed positive COVID-19 cases are also reviewed.

**Conclusion:** There is a correlation between telomere length and COVID-19 infection with higher susceptibility of elderly patients and males due to shortening in their telomere length. Approximately 53% of (111,428) infected cases ( $\geq 50$ ) years old are males, and 47% of (111,428) infected cases ( $\geq 50$ ) years old are females.

## ABBREVIATIONS

Akt: Protein Kinase B; BatCov: Beta Coronavirus; CD8CD28: Cluster of Differentiation 8, Cluster of Differentiation 28; COVID-19: Novel Coronavirus Disease 2019; CRP: C-Reactive Protein; DNA: Deoxyribonucleic Acid; DDR: DNA Damage Response; IL: Interleukins; IL- $\beta$ : Interleukin1 Beta; IL-6: Interleukin-6; NF- $\kappa$ B: Nuclear Factor- $\kappa$ B; NF-B: Family of Transcription Factors; PI3k: Phosphoinositide 3-Kinase; RNA: Ribonucleic Acid; ROS: Receptive Oxygen Species; SARS-Cov: Severe Acute Respiratory Syndrome Coronavirus; STAT1/STAT3: Signal Transducer and Activator of Transcription 1/3; TERRA: Telomere Repeat-Containing RNA Termed; Tert: Telomerase Reverse Transcriptase; Terc: Telomerase RNA Component; TNF- $\alpha$ : Tumor Necrosis Factor  $\alpha$ ; TRF: Telomere Restriction Fragment; WHO: World Health Organization

## INTRODUCTION

Telomere is a non-coding part of DNA sequences at the end of each chromosome. Mammalian telomeres contain 5-8 nucleotides with reduplicated sequences of TTAAGGG. Their functions include recognizing the end of chromosomes, avoiding the end of the chromosome from being adhesive, protecting the chromosomal ends from inaccurate connection and corruption, appropriate chromosome site in a nucleus, and synthesizing the end of chromosomes in DNA replication [1]. Telomeres are a simple DNA sequenc composed of a large number of repeats called

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**DOI:** 10.37871/jbres1159

**Submitted:** 09 October 2020

**Accepted:** 11 November 2020

**Published:** 12 November 2020

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### OPEN ACCESS

**Subjects:** Biology

**Topic(s):** Infectious Diseases, Virology, Genetics

### Keywords

- Sex variations
- Age variations
- Shortened telomere length
- Respiratory viral infections
- COVID-19

(TTAGGG) in vertebrates mainly humans. Telomeres are surrounded by a protein component called shelterin or telosome. Shelterin or telosome has an important function in the regulation of telomere length and chromosomes' protection [2,3]. Telomeres and their associated proteins can protect every chromosome end against terminal DNA degeneration, chromosomal recombination, and fusion [4]. Moreover, accelerating telomere shortening is induced by inflammation, exposure to infectious pathogens, and oxidative stress, which damage telomeres and diminish their repair mechanisms. Thus, people who were exposed to viral infections have shorter telomeres. Infectious diseases, for example, decrease telomere length and, hence, increasing the susceptibility to infection [5].

Coronaviruses are a large family of viruses that affect the respiratory tract of animals and humans [6]. They can be zoonotic, which means they can be transmitted from animals to humans. Common signs and symptoms of the disease include respiratory indications, fever, cough, weakness of breath, and difficulty breathing. In other severe cases, the disease can lead to pneumonia, Severe Acute Respiratory Syndrome (SARS), kidney failure, and even death [7]. Furthermore, coronaviruses are enveloped positive-stranded RNA viruses and characterized by club-like spikes that extend from their surface, an abnormally huge RNA genome, and a unique replication technique, which belongs to the family "Coronaviridae" and the order "Nidovirales" [6]. According to WHO, COVID-19 first appeared in December 2019 in Wuhan, China. Bioinformatic analyses revealed that COVID-19 has characteristics that are typical to the coronavirus family and belong to the  $\beta$ -coronavirus 2B lineage. On the other hand, the genome sequence of the COVID-19 virus and other available genomes of  $\beta$ -coronavirus showing the closest relationship with the bat SARS-like coronavirus strain BatCov ratg13, identified 96% [8].

The primary purpose of this review is to identify the correlation between telomere shortening and susceptibility to COVID-19 infection, by investigating the changes in telomere length according to variations in age, sex in confirmed cases with COVID-19 infection, and the relation between the inflammatory markers and telomere length during respiratory viral infection.

### Telomere length changes according to age and sex

Many studies have shown that age, gender, current health status, and mortality may affect telomere length that varies within the same group [9]. Telomere shortening is considered as an important biomarker (biological thermometer) [10]. Since it might be related to the replication problem phenomena, which says that DNA polymerases are not able to replicate in the linear chromosome that leads the telomeres to shorten after each cell division, consequently, this may be followed by cell death [11].

### Telomere and sex

There is an association between sex and telomere length [12]. Previous studies clarified the association between sex and telomere length especially in leukocyte telomeres which are longer in women than men [13]. Several hypotheses have been postulated to explain this association, for example, due to the action of estrogen [14]. An estrogen-responsive element is present in Telomerase Reverse Transcriptase (hTERT), subsequently, estrogen might stimulate telomerase to add telomere repeats to the ends of chromosomes [15]. Telomeres are particularly sensitive to oxidative stress [16]. Women produce fewer reactive oxygen species than men due to high level of estrogen in female than males [15]. So, it has been suggested that women might also metabolize reactive oxygen species better because of the antioxidant properties of estrogen [15]. At birth, one study found that there was a difference in telomere length between the sexes with female newborns have longer telomeres than males [17]. An animal study on mice (males and females) indicated that the repeated experimental inoculation resulted in systemic infection and disease with higher susceptibility in males than females [5]. Moreover, they examined in the previous study the changes in telomeres in WBCs over nine months and five consecutive infections and found that the experimentally infected males showed significantly greater telomere attrition compared to female infected controls; unlike males, the infection did not affect the telomeres of the females, this sex-difference in telomere dynamics could be due to the higher susceptibility of males leading to greater infections than females [5]. There are concerns about the robustness of telomere length as a biomarker of aging [18,19]. In conclusion, telomere length is longer on average in females than males and the strength of these associations varies by the measurement methods but not by age group [13].

### Telomere and age

A steady decline in telomere length at a relatively constant rate with advancing age has been demonstrated in various cross-sectional studies. This decrease in length is further accelerated with the onset of several diseases that develop with aging [20]. Various studies on human models have attempted to correlate between telomere length with age; a study accentuated that individuals with long telomeres lived longer than their counterparts with the same age and had shorter telomeres [21]. However, the presence of short telomeres among young people [22,23] might result from many factors as genetics modifications, [21,22] chronic psychological stress [24,25], older paternal age at conception [26], poor health behaviors, and oxidative stress. The reason behind these discrepancies is still unclear and may have several causes. A conclusion from previous various studies is that telomere length correlates with somatic cell growth till puberty and with cellular senescence after puberty [27].

### Characteristics of COVID-19 infection

At the end of December 2019 in Wuhan, China, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) appeared with confirmed human cases [28,29]. It spreads rapidly worldwide causing a pandemic of Coronavirus Disease (COVID-19). Symptoms range from fever and breathing difficulty to pneumonia and death [30]. Patients have COVID-19 show increased leukocyte numbers, and elevated levels of plasma proinflammatory cytokines in blood. Cytokines and chemokines which noted in patients with COVID-19 infection include [ IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA ]. Some severe cases show high levels of pro-inflammatory cytokines as [IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα] that are reasoned to increase the severity of infection.

### COVID-19 variations according to age and sex

From the beginning of the outbreak of SARS-CoV-2 in December 2019 in Wuhan, China, many press articles discussed the correlation between age and gender and susceptibility to COVID-19. So, to prepare this review, we use a published data about all confirmed positive cases included the age and sex as showed in (Table 1). The data is from nine countries and cities Mainland China [31], South Korea [32], Japan [33], Philippines [34], Finland [35,36], California, USA [37], Italy [38], Czechia [39], and Estonia [40].

The age groups are classified by using 10-years intervals: 0-9, 10-19, 20-29..., 70-79, and ≥ 80 years old. In addition to unknown cases, so the total of 10 age groups are

designated. The sex groups are classified into male, female, and unknown.

We analyzed the known data according to the age groups as in figure 1, according to sex groups as in figure 2 and according to the age and sex groups together as in figure 3.

### Telomere length in response to viral infection

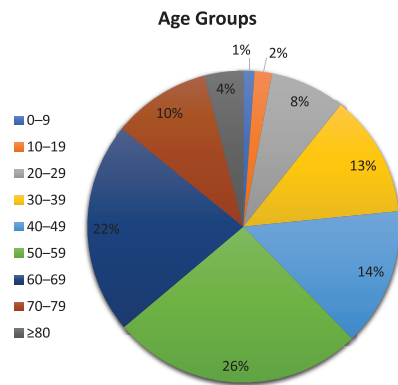
Telomeres are repetitive elements at the ends of linear chromosomes that are essential for maintaining genomic stability [41,42]. Telomere repeats can be transcribed to make a non-coding RNA, Telomere Repeat-Containing RNA Termed (TERRA), that has been identified in numerous organisms, and contributes structurally and functionally to telomere regulation [43,44]. TERRA can be induced in response to various types of stress [45,46], including DNA damage and viral infection.

### Telomere length changes during DNA viral infection

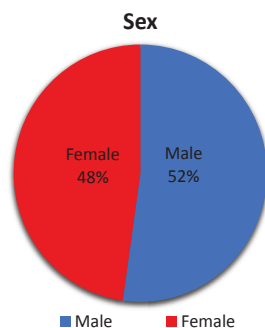
DNA viral infections can activate a DNA Damage Response (DDR) signaling pathway similar to the chromosome double-strand break or an uncapped telomere [47]. In the same way as the telomere, viruses have many mechanisms to avoid the DDR, including the assembly of the protective complexes of viral DNA ends that can actively inhibit the cellular DDR [48]. Several acute nuclear DNA viruses and one RNA virus were found to increase TERRA expression [49]. Telomeres are responsive to various stress response pathways, including viral infection, reactive oxygen species [46], and DNA damage signaling [50]. Consequently, TERRA transcription can also be induced by p53 activation, thus,

**Table 1:** Show all confirmed positive cases in Mainland China, South Korea, Japan, Philippines, Finland, California, Italy, Czechia and Estonia.

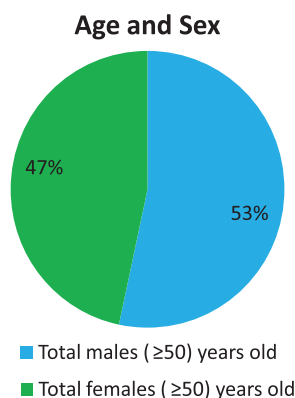
Characteristics	Country/City								
	Mainland China	South Korea	Japan	Philippines	Finland	California	Italy	Czechia	Estonia
<b>Till date</b>	February 11, 2020	April 1, 2020	March 22, 2020	April 2, 2020	April 2, 2020	March 25, 2020	April 1, 2020	July 13, 2020	July 13, 2020
<b>Ages (year)</b>									
0 - 9	416	116	12	6	21	37	1,437	840	30
10 - 19	549	519	4	15	62			1159	78
20 - 29	3,619	2,682	84	206	228	1,505	26,489	1852	193
30 - 39	7,600	1,027	92	325	272			2219	263
40 - 49	8,571	1,323	142	329	299			2631	348
50 - 59	10,008	1,865	187	496	324	1,442	74,433	1552	426
60 - 69	8,583	1,245	171	543	160			1026	253
70 - 79	3,918	658	138	290	102			671	252
≥80	1,408	452	93	102	50			409	171
Unknown	-	-	-	323	-	22	-	815	-
<b>Sex</b>									
Male	22,981	3,946	520	1425	778	1,665	56,673	6497	685
Female	21,691	5,941	403	885	740	1,309	45,996	5862	812
Unknown	-	-	-	323	-	32	-	815	517
<b>Total</b>	44,672	9,887	923	2,633	1,518	3,006	102,669	13,174	2,014



**Figure 1 Age Groups.** Pie chart of the age of known, confirmed, and positive cases in Mainland China, South Korea, Japan, Philippines, Finland, California, Italy, Czechia and Estonia.



**Figure 2 Sex.** Pie chart of the sex of known, confirmed, and positive cases in Mainland China, South Korea, Japan, Philippines, Finland, California, Italy, Czechia and Estonia.



**Figure 3 Age and Sex.** Pie chart of the (≥50) years old infected known, confirmed, and positive cases in Mainland China, South Korea, Japan, Philippines, Finland, California, Italy, Czechia and Estonia.

binding sites for p53 have been identified in human subtelomeres by Chip-Seq [51]. While TERRA can be induced to high levels in response to various stresses including DNA damage and viral infection, its potential function

during viral infection remains unknown. In an experimental study, an association between shorter telomeres and upper respiratory viral infection was found [52]. CD8CD28 was the only cell population in which shorter telomeres were related to a higher risk of clinical illness like a viral infection, where the association between CD8CD28- telomere length and infection increased with age [53].

### Telomere length changes during RNA viral infection

Viruses with single-stranded RNA, enveloped as (Togaviridae, Flaviviridae, and Coronaviridae) or non-enveloped as (Astroviridae, Caliciviridae, and Picornaviridae) [54] can attack human cells at any time. Enveloped viruses (like coronavirus) the envelope fuses with the endosomal membrane, releasing viral genome into the host cytosol [55]. Although viruses can replicate in multiple types of cells, the pathological outcome manifests in only one or a few specific cell/tissue types [56]. Coronavirus infections usually start benign causing self-limiting mild flu-like symptoms. Severe acute respiratory syndrome Coronavirus (SARS-CoV), which jumped the species barrier through gaining slight genome mutations, are severe human pathogens [57]. SARS-CoV mainly infects lung cells stimulating an often-fatal inflammatory response, which is clinically called Acute Respiratory Distress Syndrome (ARDS) that begins with severe hypoxia, pulmonary edema progressing to systemic inflammation, and failure of multiple organs, culminating in a high rate of mortality [58-61]. Shorter Peripheral Blood Leukocyte (PBL) Telomere Length (TL) is associated with higher mortality among patients with ARDS and more severe lung injury. Highly significant positive associations between telomere length and lung function, shorter telomeres were seen in patients with lung function diseases compared with healthy patients [62].

### The relation between RNA virus and TLR signaling

Pattern Recognition Receptors (PRRs) are the proteins, communicated by an assortment of cells, which are dependable for detecting the presence of microbial attack. The individuals of these receptor families can be recognized by ligand specificity, cellular localization, and actuation of unique, but meeting, downstream signaling pathways [63]. PRRs are known to be activated by invasions of RNA viral infection. Toll-Like Receptors (TLRs) are the foremost broadly studied family of PRRs so far, and they are of considerable significance within the initiation of an antiviral reaction upon disease. The human TLR multigene family comprises 10 individuals, of which TLR 2, 3, 4, 7, and 8 are thought to be of importance within the recognition of basic components of RNA infections, counting viral double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), and surface glycoproteins [64].

Toll-Like Receptors (TLR) 7 and 8 are intracellular sensors found in endosomes that recognize single-stranded RNA. Both sorts of receptors induce the expression of pro-

inflammatory cytokines and sort I IFN reaction upon RNA viral infection sensing [65,66]. TLR7 and TLR8 activated differential signaling cascades that contributed to the particular phenotypes observed. It has been found that FOSL1 restrained sort 1 cytokines after TLR7 signaling and revealed the part of TLR7-dependent Ca<sup>2+</sup> flux in modulating sort I IFN reactions. It is illustrated that although both TLR7 and TLR8 recognize single-stranded RNA, they activated diverse signaling pathways in human monocytes that contribute to particular phenotypes during RNA infection disease. In addition, it is characterized by individual targets inside these pathways that advanced particular T helper and antiviral reactions [67]. TLR7 activation induces a Th17-polarizing phenotype whereas TLR8 incitement actuates a Th1-polarizing phenotype on human CD14<sup>+</sup> monocytes. The diverse effects of TLR7 and TLR8 inhibition on pro-inflammatory cytokine expression and sort I IFN responses led to hypothesize that TLR-7 and TLR-8 incitement initiate distinctive functional phenotypes on CD14<sup>+</sup> monocytes. To test this speculation, Imiquimod (IMQ) has been chosen as a human TLR7-specific ligand and ssRNA<sub>40</sub>-LyoVec (ssRNA<sub>40</sub>) as a human TLR8-specific ligand and stimulated ex vivo confined CD14<sup>+</sup> monocytes with them to examine the expression of pro-inflammatory cytokines [68].

### Telomere length and telomerase activity

An important type of proteins related to telomere is called Telomerase Reverse Transcriptase (TERT), which is encoded by the “Tert” gene that specifically recognizes the 3′-OH group at the end of G-rich strand overhang. This arrangement is decided by the action of telomerase, which lengthens terminal regions of eukaryotic telomeric DNA by RNA-templated addition of the repeated DNA arrangement. Complete replication of telomeric DNA requires telomerase [41]. This polymerization activity was then appeared to happen on natural telomeres *in vivo* which initially called ‘telomere terminal transferase [69]. Telomerase could be a specialized cellular RT. It is a Ribonucleoprotein (RNP) complex, it synthesizes one strand of the telomeric DNA - namely, the strand running 5 to 3 towards the distal end of the chromosome—by replicating a short format arrangement inside its natural RNA moiety. This activity extends the 3 terminal, single-stranded overhang found at the closes of telomeric DNA [70]. Several Studies reported the link between oxidative stress and telomere shortening. Telomerase neutralizes telomere shortening and cellular senescence in germ, stem, and cancer cells by including repetitive DNA arrangements to the ends of chromosomes [71].

### C-reactive protein

C-Reactive Protein (CRP) is a pentameric protein circulating in blood plasma which is a marker of inflammation [72], besides, being a member of the pentraxin family of proteins [73]. CRP is synthesized by the liver in reaction to components discharged by macrophages and fat cells

(adipocytes) [74]. There are various causes of a raised CRP. These include acute and chronic conditions, and these can be infectious or non-infectious in etiology [75]. However, markedly elevated levels of CRP are most often associated with infectious causes like respiratory viral Infection. CRP reaches an abnormal level in patients tested positive to respiratory viral infection. An obvious increase in CRP level was noted during specific respiratory viral infections with more prominent increases observed in elderly patients [75]. CRP inversely correlates with leukocyte telomere length [71]. Hence, during respiratory viral infections, leukocyte telomere length becomes shorter.

### Pro-inflammatory cytokines

Inflammation is one of the complex biological responses by the immune system to neutralize the damages caused either by injury or microbial infection. Pro-inflammatory cytokines are produced mostly by the activated macrophages and are involved in the up-regulation of inflammatory reactions such as interleukins (IL-1 $\beta$ , IL-6) and TNF- $\alpha$  [76].

Interleukins (ILs) are a type of cytokines that play essential roles in the activation and differentiation of immune cells. They also have pro-inflammatory and anti-inflammatory properties [77]. Interleukins consist of a large group of proteins that can get many reactions in cells and tissues by binding to high-affinity receptors on cell surfaces [78]. One of ILs is called Interleukin-6 (IL-6) that is synthesized by T and B lymphocytes, fibroblasts, and macrophages [79]. IL-6 is a pleiotropic cytokine produced in response to tissue damage and infections. IL-6 is increasing at the site of inflammation and plays a key role in the acute phase response [80]. Shorter telomeres are associated with higher IL-6 [81]. Increasing the production of cytokines has been shown to adversely affect telomerase activity and telomere length [82]. An experimental study showed that STAT3 was synergistically activated by IL-6 and TNF- $\alpha$ . STAT3, STAT1, and NF- $\kappa$ B formed triplet complexes with IL-6 and TNF- $\alpha$  stimulation, thereby increasing telomerase activity by binding to hTERT promoter more tightly [83]. Cell-level invasion assay revealed that cytokine treatments contributed to the cell invasiveness. Combined treatment of IL-6 and TNF- $\alpha$  synergistically phosphorylated transcription factors STAT3 [84]. STAT3, STAT1, and NF- $\kappa$ b physically interacted upon the cytokine stimulation. STAT3 was bound to the promoter region of hTERT. IL-6 and TNF- $\alpha$  stimulation further enhanced STAT3 binding affinity and increase the activity of telomerase [85]. The immune system dysfunction/accelerated maturing observed in chronic conditions are associated with telomeres and telomerase activity. Numerous analysts documented relationships between lower telomerase activity and/or shorter telomeres in immune system cells and raised cytokines in blood serum from patients with a chronic disorder.

### Reactive oxygen species

Several Studies reported the link between oxidative

stress and telomere shortening. Telomerase neutralizes telomere shortening and cellular senescence in germ, stem, and cancer cells by including repetitive DNA arrangements to the ends of chromosomes. Telomeres are susceptible to damage by Reactive Oxygen Species (ROS) [86]. Based on *in vitro* studies, ROS have been proposed to inhibit telomerase activity [87,88].

## CONCLUSIONS

During the last years, many studies have continually provided evidence that links shortened telomeres with common respiratory viral diseases, infection risk, and longevity. Telomeres were considered as a potential biomarker that could evaluate the susceptibility to a specific pathogen as SARS-COV-2. The previous studies also provided an association between sex and telomere length, especially in leukocyte. Many studies on adults have found that the female telomere length is longer than the male ones, and one study explained that female newborns have longer telomeres than males. Males were somewhat more susceptible to infection than females this may due to greater telomere attrition in males than females.

According to the reviewed data, we found that: (1) 52% of total infected cases are males, and 48% of total infected cases are females; (2) 62% of total infected cases are ( $\geq 50$ ) years old; (3) approximately 53% of (111,428) infected cases ( $\geq 50$ ) years old are males, and 47% of (111,428) infected cases ( $\geq 50$ ) years old are females. The previous results approve that elder males are the most susceptible to COVID-19 infection.

Patients have COVID-19 show an increase in leukocyte numbers, and increased levels of plasma pro-inflammatory cytokines as IL- $1\beta$ , IL-6, and TNF- $\alpha$  in blood and an elevation in the production of cytokines has been shown to adversely affect telomerase activity and telomere length. For example, shorter telomeres are associated with higher IL-6. CRP rises to an abnormal level in patients tested positive to a respiratory viral infection and CRP inversely correlated with leukocyte telomere length. Unfortunately, there is a lack of data that discussed the relationship between telomerase activity and CRP. All markers of inflammation provide the relation between telomere length and COVID-19 infection.

## ACKNOWLEDGMENT

We are very pleased to direct special thanks to people who kept checking our progress and directed the review process, Dr. Mennatallah Abdelkader, Department of Microbiology and Immunology Faculty of Pharmacy Suez Canal University; Ahmed Ibrahim Sorour, Pharmacy graduate, Damanhour University; Dr. Marwa El-Araby, Medical Microbiology & Immunology Department, Faculty of Medicine, Benha University; Dr. Ahmed Ibrahim, Pharmacognosy Department, Faculty of Pharmacy Suez Canal University.

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**How to cite this article:** Kamal MA, Alamiry KR, Zaki M. Sex and Age Differences in Telomere Length and Susceptibility to COVID-19. *J Biomed Res Environ Sci.* 2020 Nov 12; 1(7): 303-310. doi: 10.37871/jbres1159, Article ID: JBRES1159