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Review

Physiological Stress as Risk Factor for Hypersensitivity to Contrast Media: A Narrative Review of the Literature and a Proposal of Psychophysiological Tools for Its Detection

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Abstract: The use of contrast media in clinical diagnostic practice has increased significantly in recent years, accompanied by an increase in adverse reactions. These are the fleeting symptoms most complained about by patients: Flushing of the face, feeling of nausea, and heat lasting a few seconds, considered side effects related to the drug. Hypersensitivity reactions are rarer but dangerous and are driven by the immune system. To ensure the optimal management of adverse reactions to iodinated contrast media, various types of health specialists, such as radiologists, are looking into how to deal with the problem. While there are many suggestions in the scientific literature on what to do in the case of important reactions during or after radiological examination, unfortunately, there are no studies on primary and secondary prevention and, in particular, on psychophysical and psychophysiological influences. Some inferences could be made by observing the studies about psychophysiological stress and immune-inflammatory processes of allergies. The few studies in the literature on the analysis of processes affecting both psychophysiological stress and allergic responses have been analyzed. Finally, stress measurement methods are proposed that can highlight "hypersensitive" people with physiological characteristics capable of exacerbating or accentuating an allergic reaction to contrast media.

Keywords: contrast media; adverse reactions; stress; psychophysiology; primary and secondary prevention

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1. Introduction

In the literature, there are many references and studies regarding adverse reactions to different contrast media, so much so that the American College of Radiology (ACR) has deemed it appropriate to publish a specific manual of over 130 pages on these topics. Contrast agents are among the most used drugs in the world (an estimated 75 million examinations with iodinated contrast agents per year), and adverse reactions concern 1–3% of administrations [1]. Therefore, the number of people who complain of adverse reactions is more than considerable. To ensure the optimal management of adverse reactions using iodinated contrast media, radiologists and allergists tackle the issue together through both fervent scientific debate and direct comparisons. However, little attention has been devoted to hypersensitivity due to personal situations of chronic stress and to the psychophysiological alteration of the individual such as to favor important allergic reactions.

Contrast media is widely used during the execution of instrumental investigations (CT and resonance and more recently in ultrasound scans). The most used are iodinated contrast media, useful in differentiating normal areas from pathological ones. Unfortunately, some side effects are described in the scientific literature. For instance, side effects of iodine contrast can include a skin rash or hives, itching, headache, nausea, and vomiting [1–3]. Symptoms can also include difficulty breathing, a rapid heart rate, and swelling of the throat [2–4]. All these reactions and other symptoms and disorders are well known in both clinical and research fields. The ACR Manual on Contrast Media of the American College

of Radiology [1] suggests that all clinicians must consider allergic-like reactions to modern iodinated and gadolinium-based contrast mediums. In fact, there are several risk factors that increase the likelihood of a reaction, minor or severe [2].

The iodinated contrast media are compounds of 2, 4, 6 tri-iodobenzoic acid. They are classified as ionic and non-ionic [1–3]. They can have high osmolality (ionic monomers) or low osmolality (ionic dimers, non-ionic monomers such as iopromide, and non-ionic dimers). Osmolality, viscosity, and iodine content are closely related, and it is known that adverse effects increase with greater osmolality [5,6]. Therefore, in clinical use, non-ionic dimers are preferred due to their lower osmolality and lower chemotoxicity. However, these compounds have negative characteristics because they are more viscous than non-ionic monomers and more expensive. Furthermore, their administration is not without risks, for example, in subjects with impaired renal function [7–10]. Another compound used is Iopamidol, a widely used non-ionic monomer with an osmolality twice that of plasma at a concentration of 300 mg of iodine/mL, while iodixanol is a non-ionic dimer, which, at a concentration of 300 mg of iodine/mL, has an osmolality approaching that of plasma (290 mOsmol/kg). However, due to its high cost, it is used only in cases where osmolality is deemed capable of altering the quality of the examination (e.g., coronary angiography with cardiac CT and lower limb angiography for severe ischemia) [11].

The various contrast media used in medical radiological diagnostics can cause adverse reactions or side effects of various types and of varying severity.

In general, contrast agent reactions can be classified into two groups [12,13]:

1. Reactions of a chemotaxic nature or of Type A: So-called because the toxicity of the compound is linked to its chemical composition. These reactions are predictable as well as closely related and dependent on the type of contrast medium used and the dose administered [12,13].
2. Unpredictable or Type B reactions: These are reactions in which the cause–effect relationship is much more difficult to establish. To explain them, various hypotheses have been made regarding the intervention of the immune system, the presence of concomitant diseases, and the current emotional state of the patient [13]. The latter is not dependent on the type of medium used and the administered dose.

Symptoms reported by the patient can vary greatly, so the adverse reactions are divided into [14–16]:

1. Mild: Pain at the injection site, urticaria (but limited to the same site), nausea, vomiting, and sweating. These reactions generally do not require specific treatment.
2. Moderate: Diffuse urticaria, severe vomiting, edema (swelling) of the eyelids, dyspnea, and pain in the chest and abdomen.
3. Severe: Pressure drop with collapse, heart rhythm alterations, severe dyspnea, larynx and lung edema, neurological symptoms with convulsions, and loss of consciousness until death.

Moderate or severe reactions always require immediate therapy with adrenaline, cortisone, antihistamines, bronchodilators, and possibly respiratory assistance. Unfortunately, it must be said that, although quite rare, adverse reactions from contrast media can lead to the death of the patient.

There are also situations of clinical interest that must be acknowledged, such as in cases of severe renal and hepatic insufficiency [16,17]. The scientific literature on the subject agrees that in renal insufficiency, it is necessary to avoid the use of the contrast medium and to opt for alternative investigations (ultrasound, magnetic resonance) [9,16].

Finally, it is also recommended by many researchers to pay diagnostic attention to other subjects considered at risk, such as those who have had allergic reactions, suffer from asthma, or have had previous reactions to iodinated contrast media [17,18].

Hypersensitivity Reactions

Hypersensitivity reactions to low osmolar contrast media involve approximately 3% of people, and in 70% of them, the most reported manifestations are erythema and urticaria, with or without angioedema [1,18]. Anaphylactic reactions are rare, with an incidence ranging from 0.004% to 0.01% [18]. Moderate to severe reactions also include bronchospasm and dyspnoea, angioedema, coronary spasm, hypotension, arrhythmia, heart failure, and loss of consciousness [16–18]. Mortality is low, from 1 to 3 per 100,000 administrations, for both ionic and non-ionic contrast media [3,11,18]. In elderly subjects, mortality associated with contrast media is considerably higher, while children are more sensitive to changes in fluid volume following the administration of contrast media [13,18]. Even very small doses of iodinated contrast media can trigger a reaction, so it is not recommended to carry out test injections [19].

Reactions can arise immediately, but delayed reactions after 1 h, or sometimes even up to a week, may also occur [18]. These reactions (2–5%) are not due to anaphylaxis but are possibly T-cell mediated and may consist of maculopapular rash, urticaria, and angioedema [20].

Osmolality is strongly associated with adverse reactions. The most important risk factor is a previous reaction to contrast media with an absolute risk of 20–60% during subsequent exposure. Previous disorders, such as asthma, significantly increase the risk [18–21]. Previous therapy with beta-blocker drugs has also been associated with hypersensitivity and may further worsen a bronchospasm reaction [18–20]. Moreover, a history of multiple allergies requiring treatment increases the risk of acute reactions to iodinated contrast media by 3–5 times [18,20].

Vasovagal reactions may also occur during the infusion [22,23]. Typically, they are treated with lower limb lifting and the administration of 0.6 mg of atropine. Mild delayed hypersensitivity reactions are then usually treated with an oral antihistamine. Reactions associated with bronchospasm and dyspnea, laryngospasm and stridor, or hypotension are treated immediately with epinephrine, intravenous fluids, and oxygen, as well as antihistamines. In severe cases, it may be necessary to carry out intubation and supportive therapy that can continue for several days [11,18,22,23]. Most patients recover in each case with no further sequelae [23].

Another reaction to contrast media well described in the literature is Thyrotoxicosis. Thyrotoxicosis induced by iodinated contrast media is a rare reaction in healthy people; in fact, iodine does not have a significant effect in patients with normal thyroid function. Instead, in patients with Graves' disease and multinodular goiter, the risk is higher, and patients with hyperthyroidism may develop a thyroid crisis [24,25].

In recent years, the percentage of reactions, especially moderate and severe ones, has decreased considerably thanks to the introduction of new compounds with greater tolerability [26,27] (Table 1).

Table 1. Risk estimation.

1. CT scan dye side effects were 0.45%
2. MRI dye side effects were 0.6%
3. 19% patients had a severe side effect (requiring medication, treatment)
4. mortality risk of 0.001%

Immediate adverse effects of high-osmolar contrast media have been reported among 12.7% of patients. With the advent of low-osmolar contrast material, this number has decreased to 4.1% of patients. Overall, mortality was estimated in 2009 in Italy to be less than 1% [26,27].

The European Society of Cardiovascular Radiology (Table 2) reports other similar recent data on the incidence of acute adverse events after the use of contrast media [28].

Table 2. Incidence and type of acute adverse events.

Category	Severity	Specific Adverse Event	Total (N = 72,839)	No Stress (N = 54,285, 74.5%)	Stress (N = 18,554, 25.5%)
No			72,579 (99.64)	54,165 (99.78)	18,414 (99.25)
Yes			290 (0.66)	120 (0.22)	140 (0.75)
Physiologic adverse events (N = 184, 71%)	Mild	Back pain	2 (0.003)	1 (0.002)	1 (0.005)
		Emesis	17 (0.023)	11 (0.020)	6 (0.032)
		Heating	6 (0.008)	2 (0.004)	4 (0.022)
		Others	4 (0.005)	-	4 (0.022)
	Moderate	Anxiety	17 (0.023)	4 (0.007)	13 (0.070)
		Angina pectoris	13 (0.018)	4 (0.007)	9 (0.049)
		Dyspnea	88 (0.221)	26 (0.048)	62 (0.334)
		Symptomatic bradycardia	12 (0.016)	4 (0.007)	8 (0.043)
		Symptomatic hypertension	2 (0.003)	2 (0.004)	-
		Symptomatic hypotension	6 (0.008)	4 (0.007)	2 (0.011)
	Severe	Arrhythmia	13 (0.018)	11 (0.020)	2 (0.011)
		Renal failure	1 (0.01)	-	1 (0.005)
		Resuscitation	3 (0.04)	1 (0.002)	2 (0.011)
Allergic-like adverse events (N = 96, 33%)	Mild	Hypersensitive reaction	61 (0.084)	41 (0.076)	20 (0.108)
	Moderate	Respiratory adverse event	8 (0.011)	4 (0.007)	4 (0.022)
	Severe	Severe allergic reaction	7 (0.10)	5 (0.009)	2 (0.011)

2. Methods

Two independent researchers identified studies by searching electronic databases and manually searching for appropriate published studies. The following databases were searched: Medline and Embase. The main keywords utilized in the article searches included the following: Psychophysiological stress and hypersensitivity reactions; chronic stress and hypersensitivity reactions; psychophysiological stress and adverse reaction; chronic stress and adverse reaction; psychophysiological stress and contrast media; chronic stress and contrast media. It was limited to the title, abstract, or topic, depending on the availability of search options in each database. The search was limited to journals in English. Finally, the search was limited by date: The databases were searched regarding the last 10 years. For the terms psychophysiological stress/chronic stress and hypersensitivity reactions/adverse reactions, only 7 original articles were found; for the terms psychophysiological stress/chronic stress and contrast media, no scientific articles were found. The results of the collected articles are described. Interesting implications of stress with contrast media can only be speculated.

3. Results

In the scientific literature, the close link between the stress response, the immune system, and some allergic reactions has been mentioned several times, but rarely investigated [28–31]. A research study conducted in Sweden at the Karolinska Institute [31] linked mental stress and inflammatory reactions typical of allergies [32]. Höglund and colleagues [31] wanted to investigate the determinants of immune regulation, taking into account that stress can aggravate allergic inflammation. Forty-one undergraduate students were involved and studied in a period of low stress and in association with a broad exam. The results showed that perceived stress and anxiety increased in both groups during the exam period, while cortisol only increased in the atopic group. Cytokine production decreased widely in response to stress in both groups, which was accompanied by an increase in the proportion of regulatory T cells. Thus, in students with allergies, the concentration of cytokines in the blood, produced by inflammation and mental stress, triggered a series of allergic reactions, which did not occur in healthy students. In other words, when subjects begin to be stressed, the T cells increase in number in order to carry out an anti-inflammatory action. If such a system does not work effectively in people with allergies, it is possible to explain the change in the cytokine balance observed. A group of researchers at Ohio State University [33] aimed to determine whether participants' reporting of rhinitis

allergic flares was related to perceived emotional distress, depression, mood, and cortisol changes. One hundred and seventy-nine university employees completed questionnaires on perceived stress and depressive symptoms and, through the daily compilation of an online diary for 12 weeks, monitored allergy exacerbations, stressful events (for each event the severity was quantified and associated with a "stress score"), perceived stress, and mood. Salivary cortisol levels were collected each day. Subjects who experienced two or more episodes of worsening symptoms during the 12 weeks were placed in a first group (39% of the participants) while those who reported less than two episodes of worsening symptoms were placed in a second group (61% of the participants). In the first group, higher levels of perceived stress emerged. Moreover, the results showed that not only the symptoms of allergic rhinitis are a cause of stress for patients but that the opposite relationship is also true: The increase in stress, especially if prolonged, has negative effects on the health of allergic patients, worsening related symptoms. In fact, the research revealed a significant association between high stress scores and the likelihood of acute allergic reactions (worsening of symptoms) over the course of the study. A high "stress score" did not necessarily lead to worsening of symptoms on the same day that the stressful event occurred, but it proved to be an element capable of worsening allergy symptoms after several days of stress.

Therefore, it is possible to sustain that psychological stress and negative emotions amplify immune-mediated clinical symptoms in individuals with allergic disorders [32,34]. Heffner et al. [34] investigated this aspect further. Their objective was to investigate whether anxiety and exposure to stress (in this case, the Trier Social Stress Test—TSST) affect the responses of the Skin Prick Test (SPT). The SPT wheals of patients with allergic rhinitis, evidenced by the clinical history and the SPT results, were evaluated before and after exposure to stress and then the following morning. The results showed that after the TSST, more anxious patients with atopy had a higher incidence of positive SPT reactions to antigens that had previously tested negative. They also found that anxiety was not related to the positive incidence of SPT in non-stressful conditions and that the SPT responses to histamine (positive control) or saline (negative control) were not affected. The data of this study underline that the current psycho-physiological arousal state of a patient can amplify the immune-inflammatory responses and that, in addition to the clinical history, the evaluation of anxiety and stress at the time of SPT can provide valuable information on the allergic state.

4. Discussion

Similar results were described in a review [35] involving patients with allergic asthma: The authors argue that psychological stress leads to eosinophilic inflammation of the airways through activation of the Hypothalamus–Pituitary–Adrenal (HPA) axis and the Autonomic Nervous System and therefore the secretion of stress hormones in the blood, including glucocorticoids, epinephrine, and noradrenaline. In particular, the interaction between stress and neuroendocrine activity would influence the immune responses of regulatory T cells (Tregs), which are closely related to the exacerbation of asthma.

However, it is emphasized that from the analysis in the databases considered by the researchers, no similar scientific research has emerged regarding contrast media. In fact, the focus of the studies is usually oriented to biological mechanisms and not to the so-called "neuropsychiatric phenotype". In the review of 2017 [35], the authors use this term to refer to a behavioral configuration that predisposes one to stress and, consequently, to the onset of specific stress-related physical diseases such as asthma.

Our work wants to underline the fact that only a few studies are performed in this direction and that from the analysis of the literature no studies have been conducted on the predisposition to stress and adverse reactions to contrast media. Therefore, useful considerations in the field of nuclear medicine can only be inferred. It is hypothesized that the allergic reactions described in the previous studies may resemble the responses to contrast media and thus explain, at least in part, the cause.

Considering stress as a stimulus capable of altering the homeostatic balance of an individual, it is necessary to understand everything that results from it and to use the stimuli available to measure it. In the context of clinical psychophysiology, Selye's definition of stress is a point of reference [36]. This author has favored the enrichment of this line of studies by defining stress as a functional physiological process that is activated following a subjective evaluation of the stressor. In fact, the emotional and psychophysiological activation is described in terms of General Adaptation Syndrome (GAS). According to Selye, GAS refers to the organism's response when faced with a stressor, intended as a stimulus capable of altering its homeostatic balance. More specifically, the stress reaction is a phenomenon composed of three phases. In the first phase (alarm), there is the activation of the Sympathetic Nervous System (SANS) with consequent activation of the medullary portion of the adrenal glands and secretion of adrenaline and noradrenaline. Both catecholamines increase cardiac output and, thus, increase the blood supply of skeletal muscles. The body mobilizes energy resources and directs them towards a fight or flight behavior. Furthermore, in this phase, the HPA axis is activated with the secretion of glucocorticoids. In particular, cortisol, known as the "stress hormone", triggers the conversion of proteins into glucose, involves lipids in the production of immediately available energy, increases blood flow, and activates behavioral responses. In the second phase (adaptation), the body tries to adapt to the new situation. Here there is an overproduction of cortisol, and the body organizes itself to adapt and cope with the stimulus. Finally, in the third phase (exhaustion), there are two possible outcomes: The extinction of the stress response or a condition of functional exhaustion that occurs when the exposure to the stimulus continues for a long period and the organism does not have the resources to resist and/or to adapt further. In addition, the involvement of other systems should be emphasized, namely:

The Somatotropic System: Regulates the release of the growth hormone (GH or Somatotropic hormone). Its main function is to stimulate the development of the human body, promoting the growth of cells in almost all body tissues.

- Gonadal System: Involves the interaction between the hypothalamus, pituitary, and gonads. Being fundamental for ovulation, it releases estrogen and progesterone (in females) and spermatogenesis and testosterone (in males).
- Thyroid System: Regulates the release of T3 and T4 hormones, essential for energy metabolism and tissue functions. Considering that psychophysical stress interferes with the functioning of all these systems and apparatuses, it becomes important to consider accurate tools for its measurement.

5. Recommendations

Currently, adverse events have a low incidence [1,18,28], and people at risk are, fortunately, few. However, due to the unpredictability of stressful life events that can affect people's lives and cause more or less intense stress reactions, it is not as easy to estimate how many people may be "hypersensitive" in a given period of time. In fact, a hyper activation of the HPA axis can be found in all people who manifest anxiety or depression at a clinically significant level. Actually, it is estimated that approximately 350 million people worldwide suffer from depression and 265 million suffer from anxiety, with a prevalence calculated for the entire population equal to 4.4% and 3.6%, respectively [37]. Moreover, some stressful factors can affect a large category of people at the same time, for example, the pandemic has generated a significant increase in stress levels [38–40]. Thus, the number of people who could be affected by somatic repercussions and psychophysiological stress disorders is subject to wide variation.

In any case, it is important that the health system guarantees to every person who undergoes an instrumental examination their right to Health. The term Health obviously refers to the latest definition of the WHO [41] for which it is not only the absence of disease but the achievement of the highest level of psycho-physical well-being. For this reason, even hoping that the subjects at risk are few, it is important to use the tools made available by the scientific community.

A useful and non-invasive tool for the assessment of the level of psychophysiological activation is the Psychophysiological Stress Profile (PPP), able to detect some of the physiological indices linked to ANS activation and the complex system involved in the stress response [42–47]. During PPP, different physiological parameters are recorded, and the most used are:

- Surface Electromyography of the frontal muscle (sEMG), the electric potential of which can be detected using two active electrodes placed approximately 1 cm above the eyebrows that line the pupils and a reference one in the center of the forehead.
- Heart rate (Heart Rate, HR) Heart Rate Variability (HRV), and Inter-Beat-Interval (IBI); detecting the electrical potential of the heart muscle with the classic bipolar junction. These indices are used for the electrocardiogram and for calculating the time between R waves (ventricular contractions).
- Peripheral Temperature (PT), by applying a thermistor to the base of the thenar eminence of the dominant hand.
- Skin Conductance or Galvanic Skin Response (GSR), by letting a slight electric current pass between two electrodes located on the last phalanx of the fingers of the dominant hand. Two measurements of the electrical resistance of the skin can be taken. The first is the basic resistance also known as the Skin Conductance Level (SCL), and the second skin resistance response to a stimulating situation is known as the Skin Conductance Response (SCR).
- Additional parameters, such as the Respiration Rate, or amplitude, can be collected, as well as others that describe the CNS activity as different kinds of evaluation of the electrical brain activity (EEG, EEG mapping, EP, etc.).

The methodology of PPP consists of three consecutive phases: Resting or baseline, stress presentation, and recovery. In the intermediate phase (stress), a mental task is usually requested [42–47].

The principal aim of the PPP is to verify how far the psychophysiological balance seems to be maladaptive, utilizing the observations from one or more parameters:

- High level of autonomic nervous activation in the rest phase.
- Slow, unsettled, or absent values disposition of one or more parameters during the recovery phase.
- Abnormal width of the activation stress-induced response in one or more parameters during the "stress" phase.
- Slow, unsettled, or absent values of one or more of the parameters during the mental task (stress phase).
- Slow, unsettled, or absent restoration of the values of one or more parameters in the recovery phase.

The set of evaluations will offer a picture of the basic autonomic activity under stress (a correct sympathetic–vagal balance with the acquisition, however, of more parameters strictly managed by the ANS). This will be accompanied by an evaluation of some psychological and psychopathological characteristics included in the context of the individual's personal life.

Furthermore, the psychophysiological evaluation described above fully satisfies the cost–benefit analyses. In fact, even requiring specialized personnel for the execution and analysis of the data carried out (usually they are psychologists who are experts in clinical psychophysiology and biofeedback), equipment, and software are low cost (in the order of a few thousand euros). In any case, it might be useful to precede this examination with a brief clinical-psychophysiological investigation in order to select patients at risk. For instance, a short clinical interview aimed at investigating the person's history and identifying any stressful events in anamnesis or a previous history of mental disorder could provide important information. In addition, specific psychological questionnaires can then be administered to identify some characteristics of state and trait (predisposition and current presence of anxiety, depression, somatic complaints, etc.) while other tests can be

used only in the case that there are real psychopathological relevant reactions (panic attacks, depressive crises, acting out, etc.) concomitant or immediately following the injection of the contrast medium.

In some cases, it may be useful to supplement this information with blood tests, which is also an inexpensive procedure. In particular, electrolytes (Ca, K, Mg, etc.), ferritin, and sideremia should be evaluated. Therefore, at the level of hormonal dosages, thyroid hormones (at least TSH, T4, T3), cortisol (Zenith and, if it is possible, Nadir), PRL, and, if there had been significant fluctuations in body weight in the previous period of life, GH. Many of the suggested tests are in fact good indicators of situations of chronic stress and inadequate immune defenses (among others, for example, the presence of syndromes such as depression or "exhaustion") [43,44].

To summarize, a useful strategy to avoid at least some adverse reactions is to combine the careful collection of anamnestic data with an accurate evaluation, albeit relatively short, of the psychological, psychophysiological, and psycho-neuroendocrine structure. This is all to be carried out in the period immediately preceding the examination (obviously, the exams in an emergency regime will be excluded). Therefore, the assessment of the general structure of the subject under examination regarding their ability and method of responding to stress will be extremely important.

The rationale and the main hypothesis are that negative reactions to the contrast medium may be linked not so much to the absolute toxicity of the substance but to predisposing factors at a constitutional and psychological-environmental level, which seem able to create a sort of "hypersensitivity subject" or, as claimed by other authors, "neuropsychiatry phenotype" [21].

Anyhow, further studies are needed to better understand the relationship between stress and allergic symptoms, in particular between psychophysiological activation and adverse reactions to contrast media. In the literature, there are no studies aimed at investigating this aspect, therefore repercussions at a clinical level can only be inferred.

6. Conclusions

From this work, the author wants to underline the need for studies regarding psychophysiological stress and hypersensitivity to contrast media as well as the importance of multidisciplinary and multidimensional management where the clinical-medical evaluation is supplemented by a psychological investigation. There are many studies in the literature that describe the psycho-neuro-endocrine-immunological mechanisms that play a protective role against physical diseases, such as the adequate management of stress, the capacity for emotional self-regulation, and balanced sympatho-vagal activity [48,49]. The impact of stress, some personality traits, and specific psychopathological tendencies on organic diseases such as cardiovascular events [50,51], malignancies [52–54], and neurodegenerative disorders [55–57] has been already analyzed. However, despite these reports, medicine units that benefit from the presence of psychology and counseling services are still few. This would allow the early detection of signs or symptoms of psychological distress and prevent the onset of consequences on psychological well-being. At the same time, an accurate assessment of mental state and individual stable traits could detect those psychological factors that are prefigured as risk factors for physical complications.

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