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Systematic Review

Headache Characteristic in Covid-19 Infected Patient: A Systematic Review

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ABSTRACT

Introduction: The neurotropism of COVID-19 virus has been addressed in several studies, and headache is one of the most frequent neurologic manifestations of COVID-19, with various results of characteristics and phenotype. In this systematic review, we aimed to characterize the most common phenotype of headache in COVID-19 infected patients.

Methods: A systematic literature was conducted through Pubmed, SciElo and Cochrane databases with keywords (headache[Title]) AND (covid-19[Title]), ((neurological) AND (headache) AND (characteristic)) AND (covid-19), ((phenotype) AND (headache)) AND (covid-19). We extracted the study design, demographics of subjects, and characteristics of headache (onset, site, lateralization, quality, intensity, and additional symptoms related to headache).

Results: We included 1381 subjects with COVID-19 infection who experienced headache symptoms from eligible 9 studies. The majority of our patients had headaches that occurred with COVID-19 symptoms onset (94.2%), ranging from 1 to 10 days after the first COVID-19 symptoms. The most common headache site was frontal (42.3%), followed by diffuse/ holocranial (40.1%), periorbital/retroorbital (24.2%), and temporal (23.8%), with no lateralization/occurring bilaterally (85.9%), and pain characteristic predominantly pressing and tightening (55.9%), throbbing (25.3%), and stabbing (9.8%). Headache intensity measured by VAS score ranged mild to moderate in most cases with duration mostly 1-24 h. 57% of headache patients were also accompanied by fever symptoms. Additional headache symptoms were also recorded, predominantly anosmia/ageusia, followed by photophobia/phonophobia, and nausea/vomiting.

Conclusion: Bilateral, long-lasting, with pressing-tightening characteristic headaches accompanied by fever, were more frequent in COVID-19 infected patients, in conjunction with anosmia/ageusia. These features may help physician to determine the headache related to COVID-19.

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INTRODUCTION

SARS-CoV-2 causes a variety of clinical symptoms other than respiratory symptoms. The potential effect of SARS-CoV-2 on the nervous system has been known and still continues to be studied, because COVID-19 patients also show various neurological symptoms, including headache, dizziness, hyposmia, and hypogeusia during the course of the disease [1].

Headache is one of the most frequent neurological symptoms of COVID-19 and interferes with the patient's daily life. In fact, headache can be the first symptom felt by patients when infected with SARS-CoV-2, as found by Rocha-Filho, et al., where 42.2% of patients complained of headache as the first symptom, although in most cases usually begin with other COVID-19 symptoms [2].

Patients with headaches should raise the doctor's clinical suspicion regarding the presence of COVID-19 infection. However, the current literature on headaches in COVID-19 shows a wide variety of results and types

of headache characteristics, from headaches resembling tension headaches to migraines without aura [3,4].

In this systematic review, we aim to summarize the clinical characteristics of headaches that are most often found in confirmed Corona Virus Disease 2019 (COVID-19) patients older than 17 years old, which can describe the onset of headache, association with other COVID-19 symptoms, location, frequency, duration, characteristics, and intensity of headache, response to analgesics, and duration of fever, thus helping doctors/other medical personnel identify the characteristics of headaches related to COVID-19.

MATERIAL AND METHODS

Literature Search

A systematic literature search was carried out through the Pubmed, SciElo and Cochrane databases with the keywords (Headache [Title]) AND (covid-19[Title]), ((neurological) AND (headache) AND (characteristic)) AND (covid-19), ((phenotype) AND (Headache)) AND (covid-19). Two authors independently examined article titles to identify articles that did not meet the inclusion criteria before assessing the abstract and full text of the selected studies. This study followed the "Preferred reporting items for systematic review and meta-analysis procedures" (PRISMA-P) method. This review has not been registered.

Eligibility Criteria

These specific criteria were used to select the research studies to be used. The inclusion criteria included: (1) the subject was more than 17 years old; (2) Cross-sectional/cohort study on headache and COVID-19. Eligibility criteria are (1) inpatient or outpatient subjects with confirmed acute COVID-19, either by Real Time-Polymerase Chain Reaction (RT-PCR) from respiratory swab samples and/or SARS-CoV-2 antibody examination with symptoms of disease light to heavy; (3) Headaches were not restricted to the 'Headache with systemic viral infection' criteria according to the International Classification of Headache Disorders, 3rd version (ICHD-3), any patient who complained of headache during the course of COVID-19 was included in the study. (4) Headache associated with COVID-19 was described with onset, association with other COVID-19 symptoms, location, frequency, duration, characteristics, intensity, response to analgesics, period of fever, if there, also reported. The exclusion criteria were as follows (1) editorials, letters, comments, review abstracts, conference abstracts, news articles, book chapters, case reports, and review articles (2) articles without characteristics/sites/headaches during COVID-19 infection. (3) articles with research subjects in Acute Respiratory Distress Syndrome (ARDS) conditions.

Data Extraction

Data was extracted from the articles and summarized in tables using Microsoft Excel software. Two reviewers selected papers based on relevant and appropriate titles and abstracts. The data extracted included study design, subject demographics, and headache characteristics (onset, location, lateralization, quality, intensity, and additional symptoms associated with headache).

Statistical Analysis

All essential data were gathered and documented, means and percentages were used to report numerical data variables. We utilized SPSS 20.0 for Windows for statistical analysis.

RESULTS

We included 1381 subjects with acute COVID-19-associated headache from 9 studies [5–13]. The age of the subjects was reported by different methods, four of the studies described age *mean*, and the *mean* age of the four studies was 45.5 years. From the 8 studies that included gender identity, 38.3% were male. Of the 1381 subjects, 35% of patients reported a history of a previous headache disorder prior to the current headache (migraine, tension type headache (TTH), and other types of headaches).

Headache occurred about 1 day (median) after other COVID-19 symptoms in the majority of cases (754 of 778), with the most frequent location of headache being the frontal area (42.8%), followed by the diffuse/holocranial area (40, 1%), then periorbital/retroorbital (24.2%), and temporal (23.8%). Other less frequent headache locations were occipital (17.69%), parietal (13.8%), cervical at 122/1153 (10.6%).

Around 86% of patients reported headaches that occurred bilaterally/no lateralization, but 150 patients reported headaches (13.7%) and head in the midline (0.3%). A total of 55.9% of headaches described as "pushing and tightening", followed by "throbbing" in 25.3% of cases, "stabbing" in 9.8% of cases, "burst" in 4.2% of cases, "dull" in 2.7% cases, "fiery" (like burning) (1.4%), "drill" (as drilled) at 0.5%, "shoot" (like being shot) at 0.4% of cases, and "unknown" in 0.8% of cases. Headaches were mostly mild to moderate in intensity (66.3%) the rest were severe and most responded well to analgesics. Other concomitant symptoms are fever in 58% of cases, ageusia/ hypoageusia, anosmia/ hypoanosmia, photophobia, allodynia, nausea, vomiting, worsening with physical activity, and worsening with head movements.

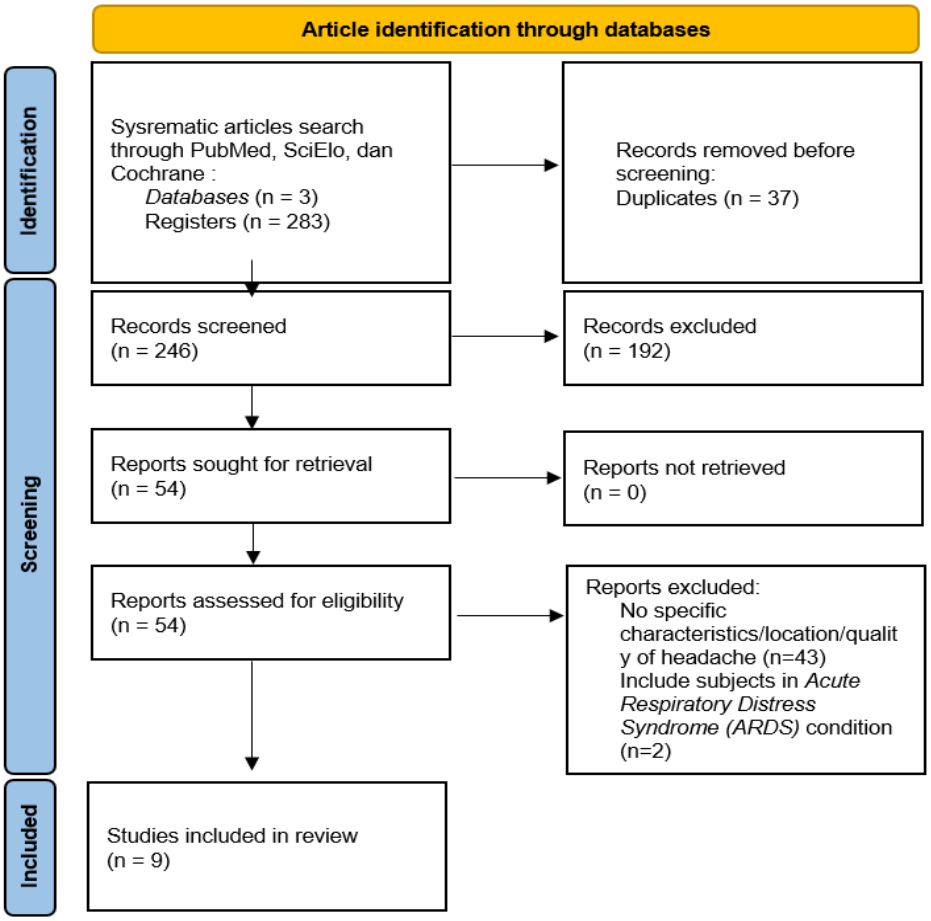


Fig.1. PRISMA 2020 Diagram of This Research

DISCUSSION

Headache is the most common neurological symptom complained by patients with SARS-CoV-2 infection. Its prevalence in various studies is very diverse. Huang, *et al,.* in his study found a prevalence of about 8% [14], a meta-analysis involving more than 40,000 patients from 60 studies estimated the average headache presentation to be around 12% (4%-23%) [15].

Headaches caused by COVID-19 are common in middle-aged individuals, and are more common in women (male subjects in this study were 38.3%). The high prevalence of female sex in headache related to COVID-19 is in accordance with previous studies by Liguori, *et al.*, who found that women report subjective neurological complaints more frequently than men [16]. The possibility of this happening is that men tend to experience more severe symptoms of COVID-19 than women, so they report headaches less often because other symptoms are felt to be more severe.

Complaints of headache as an early symptom of SARS-CoV-2 infection are also associated with a milder clinical course of the disease in terms of inflammatory markers. A study by Caronna, *et al.,* observed lower IL-6 levels in the headache group and during the evolution of COVID-19, IL-6 levels were more stable in patients with headaches compared to patients without headaches [12]. Patients with headaches associated with milder symptoms of COVID-19.

Men had higher expression of the ACE2 protein than women and contributes to gender disparities in morbidity and mortality from COVID-19 disease [17]. Higher ACE-2 expression is associated with more severe COVID-19 symptoms and higher cytokine storms. Sex hormones in women also have a protective role against severe symptoms of COVID-19 [18].

Headache phenotypes associated with acute SARS-CoV-2 infection in this study include early onset of the disease course, bilateral headaches which mainly occur in the frontal region, with qualities such as being pressed and tightly bound, mild to moderate intensity and mostly respond well to treatment. This type of pain is most likely muscle or myofascial pain, which is

characterized by a characteristic pain that is dull and achy, not localized, and bilateral.

The exact mechanism of this headache condition in COVID-19 infection is still unknown, but a hypothesis that can be considered is sensitization of pericranial or intracranial pain-sensitive structures through direct infiltration, release of endotoxins, or immune responses of inflammatory mediators due to the SARS-CoV-2 virus [11,19]. Belvis in his case report mentions several factors that may contribute to this condition, namely cervicogenic factors which cause myofascial pain due to poor posture during quarantine, stress factors due to anxiety about worsening COVID-19, and also causes insomnia due to anxiety. Headaches that resemble tension-type headaches also easily improve after taking acetaminophen [20].

Another type that is also often found is migraine which is characterized by throbbing headaches, hypersensitivity, and gastrointestinal symptoms [21]. The possible pathophysiology of this symptom is direct attack of SARS-CoV-2 on the trigeminovascular system, via transynaptic or bloodstream spread, and/or an immune-mediated inflammatory response acting on the central nervous system. Other viruses, if they share the same characteristics, may cause headache as the predominant symptom; However, a more detailed study is still lacking [22–24].

Several other studies suggest that the presence of headaches may be related to the immune response to SARS-CoV-2 and cause inflammation of the nerves, which causes headaches [3,25]. Often patients and physicians attribute fever as the cause of headache in viral infections because the onset of headache in the course of the disease is almost concurrent with other inflammatory symptoms such as fever, myalgias, asthenia, and arthralgias [26]. However, the role of inflammatory factors in causing headaches is still not known with certainty. There is a possibility that these two things are interrelated, because inflammatory mediators can also cause sensitization of the pericranial nerve pain structures. In light of these findings, we observed that headache was not always associated with the presence of fever (only 58% of patients with headache also reported fever).

An additional frequent symptom in patients with headaches related to COVID-19 is anosmia/ageusia. It was previously hypothesized that SARS-CoV-2 has neurotropic characteristics that are capable of attacking peripheral terminal nerves and entering the central nervous system via the trans-synaptic pathway. Politi et al. reported a case of COVID-19 with anosmia and MRI showing transient regional signal alternation in the olfactory bulb of the posterior rectus gyrus [27].

Within the nasal cavity, anosmia may reflect peripheral activation of the trigeminovascular system mediated by the pathogen itself, acting not only on the specialized olfactory epithelium, but also on trigeminal branches present at this level or through olfactory-trigeminal interactions [12,27–29].

The characterization of headaches related to COVID-19 revealed that patients mainly presented headaches with frontal localization, with characteristics such as pressing and tightness of mild-moderate intensity. This type of headache does not meet the criteria for acute headache associated with a systemic viral infection [30]. So it can be concluded that headache symptoms in COVID-19 patients are not limited to one particular phenotype. The existence of a population's genetic background has the potential to influence the prevalence of this neurological symptom, possibly through polymorphisms and expression levels in various tissues of the angiotensin converting enzyme 2 (ACE2), which is the receptor for Covid-19 [31]. Expression levels and expression patterns of human ACE2 in different tissues may be important for 2019-nCoV/SARS-CoV-2 infection susceptibility, symptoms, and outcome [32].

There are several limitations of this study, including the small number of studies, because there are not many articles that discuss the characteristics of headache in detail and detail. Second, this study did not assess differences in headaches currently experienced compared to those previously experienced. In addition, there is no supporting examination to ascertain whether there are other causes that cause headaches in the subject.

CONCLUSION

Bilateral headaches, lasting a long duration with characteristics such as pressure, and accompanied by symptoms of fever are more common in patients infected with COVID-19. This symptom is more common in women, with the average age being middle age. Additional symptoms that often appear are anosmia/ ageusia, followed by photophobia/ phonophobia, and nausea/ vomiting. These symptoms can help doctors to diagnose headaches related to COVID-19 during the pandemic.

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CONFLICT OF INTEREST

The author states that there is no factor of interest.

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Table 1. Clinical Demographic of Subjects

First Author	Year	Study Type	Subjects with Headache *(n)*	Age *(year)*	Gender		History of Previous Headache, n (%)			Duration of Current Headache *(days)*	*Comorbids*, n (%)		
					Male, *n* (%)	Female, n (%)	Migraine, n (%)	TTH, n (%)	Other, n (%)		Hypertension	Diabetes	Obesity
Magdy R	2020	Cross-Sectional	172	Median 33 IQR (27.3–42)	64 (37.2%)	108 (68.2%)	45 (26.2%)	46 (26.7%)	0	-	18 (10.5%)	7 (4.1%)	-
Kacem I	2021	Retrospective Observational	279	Mean 42.17 SD ±17.58	-	-	-	-	-	Median 4 IQR (2–7)	-	-	-
Dos Anjos de Paula RC	2021	Retrospective Observational	24	Mean 53.8 SD 17.44	14 (58.3%)	10 (41.7%)		6 (25%)		-	9 (37.5%)	4 (16.6%)	3 (12.5%)
García-Azorín D	2021	Cross-Sectional	458	Median 51 (IQR: 42–61)	138 (27.9%)	320 (72.1%)	83 (18.1%)	99 (21.6%)	0	Median 7 (IQR: 4–14, n=374), > 1 month after other COVID-19 symptoms in 59 subjects (12.9%)	98 (21.4%)	37 (8.1%)	-
Rocha-Filho PAS	2020	Cross-Sectional	47	Median 56; (IQR: 44–65.5)	28 (59.6%)	19 (40.4%)	10 (21.3%)	9 (19.1%)	0	Median 10.5 days (IQR: 5–18)	-	-	-
Uygun Ö	2020	Cross-Sectional	203	-	82 (40.4%)	121 (59.6%)		116 (57.1%)		-	-	-	-
Sharma M	2022	Cross-Sectional	18	-	-	-		8 (44.4%)		-	-	-	-
Caronna E	2020	Prospective Cohort	97	Mean 50.6 ± 15.3	41 (42.3%)	56 (57.7%)	19 (19.6%)	0	31 (32%)	-	-	-	-
Karadaş Ö	2021	Cross-Sectional	83	Mean 48.40 ± 15.90	48 (57.8%)	35 (42.2%)		12 (14.5%)		Mean 5.10 SD± 2.39	33 (39.8%)	14 (16.9%)	28 (33.7%)

IQR : Inter Quartile Range
SD : Standart Deviation

Table 2. Onset of Headache in Subjects

First Author	Years	Subjects with headache (*n*)	Headache onset, *n* (%)		
			Before any other COVID-19 symptoms	With or after other COVID-19 symptoms	
				n (%)	Headache onset count from first COVID-19 symptoms (days)
Magdy R	2020	172	49 (28.5%)	123 (71.5%)	-
Kacem I	2021	279	0	279 (100%)	Median 1 day, IQR (0–3)
Dos Anjos de Paula RC	2021	24	0	24 (100%)	Median 5 days, IQR (1–10 hari)
García-Azorín D	2021	458	0	428/428 (100%)	Median 1 day, (IQR 0–3, n=428)
Rocha-Filho PAS	2020	47	0	47 (100%)	1 (1.5-2)
Uygun Ö	2020	203	-	-	-
Sharma M	2022	18	8 (44.4%)	10 (55.6%)	-
Caronna E	2020	97	9 (9.3%)	89 (91.8%)	-
Karadaş Ö	2021	83	-	83 (100%)	-

IQR : Inter Quartil Range
SD : Standart Deviation

Table 3. Clinical Characteristics of Headache in COVID-19 Subjects

First Author	Location, n (%)							Lateralization, *n* (%)			Pain Characteristics, n (%)						
	Diffuse/ Holocranial	Temporal	Frontal	Occipital	Parietal	Periorbital/ retroorbital	Other	Bilateral	Unilateral	Other	Pulsatile	Pressing and tightening	Throbbing	Exploding	Dull	Burning	Other
Magdy R	91 (52.9%)	31 (18%)	40 (23.3%)	10 (5.8%)	0	0	0	-	-	-	28 (16.3%)	70 (40.7%)	0	45 (26.2%)	29 (16.9%)	0	0
Kacem I	80 (28.7)	19 (6.8)	0	20 (7.2)	0	0	"*variable*" 13 (4.7%), not specific 7(2.5%)	263 (94.3%)	16 (5.7)	0	-	-	-	-	-	-	-
Dos Anjos de Paula RC	8 (33.3%)	1 (4.2%)	12 (50%)	1 (4.2%)	0	2 (8.3%)	0	22 (91.7%)	2 (8.2%)	0	3 (12.5%)	21 (87.5%)	0	0	0	0	0
García-Azorín D	-	190/433 (43.9%)	307/433 (70.9%)	141/433 (32.6%)	136/433 (31.4%)	170/433 (39.3%)	Vertex 113 (26.2%) n=433, cervical 118/433 (27.3%)	350/437 (80.1%)	84/437 (19.2%)	Midline 3/437 (0.7%)	64/433 (14.8%)	324/434 (74.7%)	68/434 (15.7%)	0	0	9/434 (2.1%)	0
Rocha-Filho PAS	0	26 (55%)	38 (80%)	17 (36%	23 (49%)	0	0	44 (94%)	3 (6%)	0	24 (51%)	20 (43%	2 (4%)	0	0		1 (2%)
Uygun Ö	-	-	-	-	-	-	-	166 (85%)	37 (18.2%)	0	87 (42.9%)	75 (36.9%)	29 (14.3%)	0	0	5 (2.46%)	0
Sharma M	1 (5.6%)	7 (38.9%)	5 (27.8%)	2 (11.1%)	0	2 (11.1%)	Vertex 1 (5.56%)	16 (88.9%)	2 (11.1%)	0	1 (5.6%)	3 (16.7%)	0	0	14 (77.8%)	0	0
Caronna E	37 (38.1%)	0	46 (47.4%)	0	0	0	frontocervical (6.2%), hemicranial (5.2%), cervical (4.1%), total 15%	0	0	0	19 (19.6%)	68 (70.1%)	0	0	0	1 (1%)	drilling 5 (5.2%), shooting 4 (4.1%)
Karadaş Ö	0	0	45 (54%)	13 (15.6%)	0	0	frontotemporal 3 (3.6%); 22 (26.8%) parietals, periorbital, and temporal.	77 (92.8%)	6 (7.2%)	0	47 (56.6%)	21 (25.3%)	7 (8.4%)	0	0	0	8 (9.6%)

IQR : Inter Quartil Range
SD : Standart Deviation

Table 4. Onset of Headache in Subjects

First Author	Severity		Fever, n (%)	Response to Analgetic, *n* (%)				Additional Symptoms, n (%) *								
	Intensity or Visual Analogue Scale Score	Duration of each headache episodes		Use of analgetic, *n* (%)	Good	Moderate	Poor	Ageusia/ hypoageusia	Anosmia/ hyposmia	Photophobia	Phonophobia	Allodynia	Nausea	Vomitting	Worsening with activity	Worsening with head movement
Magdy R	7 (5–8)	Median 6 IQR (2–16)	120 (69.8%)	172 (100%)	56 (32.6%)	80 (46.5%)	36 (20.9%)	-	-	-	-	-	-	-	-	-
Kacem I	Mild-Moderate 165 (59.1%), Severe 110 (39.4%), unspecified/unknown 4 (1.4%)	Median 3 h (range: 15 min to 24 h)	143 (51.3%)	-	-	-	-	-	-	-	-	-	-	-	-	-
Dos Anjos de Paula RC	Mean VAS of all subjects 6 (1.83)	8 patients (33.3%) >1 days, 15 patients (62.5%)1-24 hours, 1 patient (4.2%) < 1 minutes	19 (79.1%)	23 (95.8%)	Most of the subjects reported improvement with the analgetic, but no specific number of subjects and no specific response were included			-	8 (33%)	1 (4.1%)	-	2 (8.3%)	2 (8.3%)	1 (4.1%)	17 (70.8%)	-
García-Azorín D	-	-	263/444 (59.2%)	-	-	-	-	-	269/448 (60%)	152/456 (33.3%)	147/456 (32.2%)	-	70/428 (16.4%)	21/457 (4.6%)	52/458 (11.4%)	135/433 (31.2%)
Rocha-Filho PAS	-	-	-					25 (53.2%)	24 (33%)	21 (45%)	14 (30%)	-	20(43%)	-	-	-
Uygun Ö	Mild 26.6%, Moderate 47.7%, Severe 23.4%, Very severe 2.3%	55 (27%) >48 hours, 27 (13.3%) >72 hours	104 (40%)	167 (82.4%)	70 (42.1%)	64 (39%)	32 (19.3%)	171 (84.2%)		129 (74.4%)	137 (67.4%)	37 (18.2%)	144 (71%)	-	-	-
Sharma M	Median VAS score of all subjects is 2.76 (Range 2-6)	30 minutes - 3 days	-	-	-	-	-	-	-	1 (5.5%)	2 (11.1%)	-	2 (11.1%)	1 (5.5%)	-	-
Caronna E	Mild 24.7%, Moderate 50.6%, Severe 24.7%	<=4 jam 39 (29.3%), >4 jam 21 (21.2%), konstan 48 (49.5%)	-	-	57 (58.6%) subjects reported improvement with the analgetic, but no specific number of subjects and no specific response were included			53 (54.6%)		10 (10.3%)		-	25 (25.8%)		-	12 (12.4%)
Karadaş Ö	In 39.7% subjects : Mean 84.09 SD ± 6.05; 60.3% VAS 54.80 ± 10.49	Mean 9.00 SD ± 5.20	-	-	49 (59.0%) subjects reported improvement with analgetic, but no specific number of subjects and no specific response were included			6 (7.2%)	7 (8.4%)	25 (30.1%)	23 (27.7%)	-	30 (36.1%)	5 (6.0%)	12 (14.5%)	-

IQR : Inter Quartil Range SD: Standart Deviation * Patients may report more than one additional symptom