Epidemiological effects in Amyotrophic Lateral Sclerosis from the application of a DTCP

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Abstract

This article introduces the report on the difference occurred in management of ALS patients by an Italian Public Health Care Service through 15 years with and without DTCP (Diagnostic and Therapeutic Care Pathway) during three timeframes. The article illustrates Demography, Provenance and Territorial context of the patients in charge. The formalization of the staging-based ALS DTCP appears to have increased and improved the possibility of clinical taking in charge of patients.

Introduction

The Local Health Care Unit of Piacenza got on a set-up path for the constitution of a team of professionals dedicated to the diagnosis and care of ALS patients. The team was initially composed of hospital health professionals only, such as neurologist, physiatrist, otolaryngologist, speech therapist, physiotherapist, respiratory physiotherapist. As it is well-known that ALS disorder has severe impact on both the patient and his family, causing a progressive aggravation of their quality of life due to the evolution and duration of the symptomatology, in 2009 the team is implemented with Primary Care professionals, and a first dedicated standard product is outlined. Two essential communication means were also set up: the first one, internal, dedicated to the team and consisting of Medical records shared by all members via a dedicated web intranet area; the second one, external, consisting in a brochure containing useful information for the patient and his family.

The latter is still in use nowadays and provides essential information about the disorder and the reference contact persons such as the territory and hospital case-managers.

- Although some studies do not recognize any difference between multidisciplinary taking charge of ALS patients vs the mere neurological one [1], other studies put in evidence the benefits of a multidisciplinary approach both in terms of survival and improved quality of life [2], [3], [4], [5]. The first version of the health department ALS DTCP was therefore launched in 2014. The herein illustrated data-collection could be completed following to its latest revision in 2019 [6], [7].

Unlike other diagnostic-therapeutic care pathways that are exclusively hospitalized [8], at present the team of Piacenza includes: neurologist, physiatrist, pulmonologist, neuropsychologist, psychologist, gastroenterologist, phoniatriast (FEES) and otolaryngologist (for the replacement of the tracheal cannula at home and in care facility), Home Nursing Care Coordinator (HNCC), territorial case-manager, hospital case-manager, physical therapist coordinator, dietitian, pulmonology nurse, speech therapist, occupational therapist. The special feature of the ALS DTCP of the Local Health Unit of Piacenza, on which this report is centred, is to determine the care provision to patients – both multidisciplinary and of the single professional - based on the individual grade of functional loss they are going through [9], [10]. The patient assessment method adopted by the multidisciplinary team of the ALS DTCP of the Local Health Unit of Piacenza is based on functional scales (ALSFRS-R) and follows the guidelines of the Emilia-Romagna Region [11] that define 4 patient’s areas of need (B breathing, M mobility, N nutrition, C communication) classified in the corresponding clinic stage. (See table n° 1, STAGING CRITERIA)

Demographics Of Patients In Charge To The Als Dtcp

The first evident figure is the different number of patients between the first block and the following two: from the 20 patients in charge in the 2004 - 2009 block - that is before the formal definition of the DTCP - we pass to approx. 50 patients in the second (2010 - 2014) and third (2015 - 2019) blocks for a total number of 120 patients. The number of cases is double in the second block vs the first one and then stabilizes. Also noticeable that while the first two blocks cover 5 years each, the third block covers 4 years and six months (from January 1st 2015 to June 30th 2019). It is possible to represent the number of patients of the third block as nearly equivalent, in any case very close to the second block. The average age of the first block is 65 years with a standard deviation of 6 years, the oldest patient is 80 years old and the youngest is 47 years old; in the second block the average age increases to 80 years with a standard deviation of 11 years, the oldest patient is 85 years old and the youngest is 46 years old. In the third block the average age lowers to 74 years with a standard deviation of 11 years, the oldest patient is 90 years old and the youngest is 42 years old.

The mean age of all patients is 70 years, with standard deviation of 11, the oldest one is 90 years old and the youngest 42. (See table n° 2, NUMBER OF PATIENTS)

In the first block only 5% (1 case out of a total of 20) is older than 75, 55% (11 cases out of 20) are between 65 and 75, and 40% (8 cases out of 20) are younger than 65. In the second block 29% of cases (15 out of 52) are older than 75, 42% (22 out of 52) are between 65 and 75, and 29% (15 out of 52) are younger than 65. In the third block 58,3% (28 cases out of 48) are older than 75, 16,7% (8 cases out of 48) are between 65 and 75, and 25% (12 out of 48) are younger than 65. 36,7% of all patients (44 out of 120) are older than 75, 35,8% (43 out of 120) are between 65 and 75, 27,5% (33 out of 120) are younger than 65. (See table n° 3 PATIENTS BY AGE GROUP (ABSOLUTE VALUE AND PERCENTAGE)

The personal data of the cohort confirm the expected progressive increase in disorder manifestations with increasing age [12], with over 70% patients older than 65 years, although no decrease is registered in the older age groups [13] but, on the contrary, the number of elderly patients
While in the first block the number of male and female patients is equal, in the second block there are 25 males and 27 females out of 52, in the third block the males are 23 and the females are 25 out of 47, for a total of 58 males and 62 females out of 120 patients. In the cohort of Piacenza the incidence between the two sex genders is equally distributed. This phenomenon is contrary to the expectation of a higher incidence of the disorder in males vs females according to the 1.2–1.5:1 proportion [13],[14]. This might be related to the distribution per gender of the population in the province of Piacenza where, e.g. in 2018, the incidence of females is progressively higher (age range 70 ÷ 74 females 52,9%, 75 ÷ 79 55,2%, 80 ÷ 84 58,7%, 85 ÷ 89 65,55%)

Origin
THE TERRITORIAL CONTEXT

The Local Health Unit of Piacenza is organized in three territorial Districts covering the whole geographic area of the Province of Piacenza [15]:

1. 1. The Western District, based in Castel San Giovanni, is the smallest one (76.810 residents) and includes 21 municipalities in the western side of the province of Piacenza; its longitudinal orientation extends from the plain up to the high Apennine Trebbia and Tidone valleys. 
2. 2. The District of the City of Piacenza includes the territory of the provincial capital only (103.942 residents).
3. 3. The Eastern District, based in Fiorenzuola d’Arda, is the most densely populated (106.400 residents) and includes 24 municipalities in the eastern side of the province. It is longitudinally oriented as well, and extends from the plain up to the high Apennine Arda and Nure Valleys.

The organization in districts is for administrative purposes only, with the aim to balance the congruence between healthcare demand (in terms of population, uniformity and territorial network) and offer/presence of healthcare facilities.

Aim of the district is to guarantee the essential level of assistance (ELA) for the population of any environment, through programming and assessment of the healthcare.

The historical trend of the total patients shows that in the first block 5 out of 20 patients come from the Western District (35% of the case), 8 from the City (40% of the cases) and 7 from the Eastern District (25% of the cases). In the second block 15 out of 52 patients come from The Western District (23% of the cases), 25 from the City (48% of the cases) and 12 from the Eastern District (29% of the cases). In the third block 10 out of 48 patients come from the Western District (20,8% of the cases), 20 from the City (41,7 % of the cases), and 15 from the Eastern District (31,25% of the cases; in this latest timeframe there are 3 non-HCU patients, i.e. not resident in the province of Piacenza (6,25% of the cases). (See table n°5 ORIGIN OF PATIENTS IN ABSOLUTE VALUE)

During the almost 15-year period of observation, 30 patients out of 120 come from the Western District (out of a population of 47.898 same age people in the current year ), 53 come from the City (out of 62.487 people) and 34 come from the Eastern District (out of 67.068 people). So, the first block represents 16,7% of the total patients, the second block 43,3% and the third block 40% of the total patients. 25% out of these 120 patients come from the Western District, 44,2% from the City and 28,3% from the Eastern District, 2,5% are non-HCU patients. The distribution of patients seems not to be related to population numerosness. The most numerous District shows a lower percentage of patients vs the urban zone where we always count the greatest number of patients.

Whilst the demographic origin of patients from the different Districts of the Local Health Unit of Piacenza (TABLES 5/6) responds to an administrative and organizational logic, the demography of patients coming from a given altitude zone (TABLES 7 ORIGIN BY ALTITUDE ZONE IN ABSOLUTE VALUE TOTALITY OF PATIENTS and 8 ORIGIN BY ALTITUDE ZONE IN PERCENTAGE TOTALITY OF PATIENTS) responds to a merely geographic logic and therefore to an organizational flow more correlated to the facilities available on the territory and, in a wider and indirect way, to ecological and cultural models. The three Altitude Zones (Mountain – Plain/Hill – City/Capital of province) are referred to the population of the municipal areas defined according to the parameters of the Italian National Institute of Statistics (ISTAT) · that are at the base of the codification system adopted by the Statistics Department of the Province of Piacenza is based [16] · from which the total resident Population is derived based on the sum of the five-year age classes of interest as of 01.01.2019

In coherence with the territorial number of population, the number of patients coming from Plain/Hill municipalities in absolute number seem to be the highest, while the lowest number come, of course, from the most depopulated area, the Mountain. Based on the fact that the target population in the urban area is slightly over half that of the Plain/Hill municipalities in all age ranges, the City has, in proportion, a much greater weight than the other zones in all age ranges. Moreover, the distribution-by-age of patients in charge to the ALS Team does not seem to be always consistent with the age distribution of the population in the territories of origin.
In particular, among the ALS population of the mountain, the older age group is under-represented, while the younger age group is much over-represented.

In this case, however, we must consider that absolute numbers are too low for percentages to be considered completely reliable. In the Plain/Hill and City zones the flow appears to be, at least in part, the opposite: the distribution of elderly patients seems close to the corresponding age group, while in the Plain/Hill municipalities younger age groups (both < 65 and > 75) seem to be under-represented. Among ALS patients from the city zone the middle aged group (65/75) seems to be over-represented vs the same age group of the resident population. Furthermore, the percentage point of 46.5% in the 65/75 age group is not consistent with the distribution of patients by age, whereas other age groups of patients (< 65 and > 75) seem to be consistent with the corresponding reference populations. On the totality of the followed patients in the Mountain zone, the younger ones seem to have been more frequently detected and/or sent to the ALS Team than the older ones, definitely less detected and/or sent to the ALS Team. The opposite seems to have happened in the Plain/Hill municipalities of the Province, where a greater attention seems to have been paid to older people. The age group that received the most attention in the city zone is for sure the middle-aged (65/75), with no prejudice, however, in detecting and sending to the ALS Team patients of other age groups. Generally speaking the urban area counts the greater number of patients in respect to the resident population.

comparing the number of patients coming from the different geographic/altitude zones of the Province of Piacenza as per the three segments of the cohort and based on the five-year timeframes described the research plan - block 1: 2004/2009, block 2: 2010/2014, block 3: 2015/2019 (June) - are indicative of the “historical” trend of patient detection and sending to the ALS Team. We decided not to make the comparison per cent in this table, because the absolute values per each block are too low to grant a realistic representation in percentage of the differences between the timeframes (see table n°9 ORIGIN OF PATIENTS BY ALTITUDE ZONE GROUPED BY TIMEFRAME IN ABSOLUTE VALUES). The above values show a progressive, time-related decrease of the number of patients coming from the mountain area as if they were progressively “running low”, and the older age component (> 75) still remains under-represented as previously evidenced. The figures confirm, instead, a progressively increasing attention, in the Plain/Hill zone, towards the elderly component (> 75), whose presence goes from 0 in the first block to 9 in the second block and 14 in the third block, while the trend of other age groups remains constant (< 65), except for a peak in the age range 65/75 in the second Block that returns to the previous values in the third Block. As previously noticed, the weight of the City is proportionally higher in all age groups, considering that its population is little over half that of the Plain/Hill municipalities. As well as for the Plain/Hill zone, also in the urban area the numerosity of older patient component (> 75) increases progressively over time, even though the number of patients belonging to the other age ranges remains quite stable. Just like the Plain/Hill zone, also the urban area registers a peak of patients ageing 65/75 in the second block (2010 + 2014) that returns to the previous values in the third block.

Summarizing the data relating to the altitude zone in the above tables, we can therefore assume an ever increasing detection and/or sending of patients to the ALS team from the urban territory, with an increase in the older age component, particularly evident in the Plain/Hill municipalities as well. On the contrary, the access to the service – like other facilities - seems to become more difficult for patients from the Mountain, also due to progressive depopulation.

Prevalence

The ALS prevalence Rate registered in Italy in the latest few years has been progressively increasing.

The estimated prevalence rate in Western countries at the end of the past century was around 2.7 ÷ 7.4 cases per 100.000 people (average rate 5.2 per 100.000)[17]. In the first decade of the 21st century, approx. 6 cases per 100.000 citizens were recorded [18], [19], meaning that approx. 3.600 people suffering from Amyotrophic Lateral Sclerosis were registered in Italy (referred to ISTAT census of 2011), 267 of which in Emilia Romagna [20]. In 2017 the DTCP of AISLA (the Italian ALS Association) indicates a prevalence of 6÷7 cases per 100.000 residents while the reported prevalence in Eastern Europe is 6–8 cases per 100.000 residents [21]. In February 2020 AISLA’s website reports values almost double than the above, calculated on the basis of the prevalence data supplied by EURALS Consortium (the European Amyotrophic Lateral Sclerosis consortium); this means that the number of people suffering from ALS disorder in Italy would be 6.000, 443 of which in Emilia Romagna [22].

“The variability of the collected rate values can be attributable both to the reference population – often few in numbers – and to difference in the diagnostic criteria and methods, which determine a margin of error vs the over-estimation or the under-estimation of ALS patients”[17].

ALS PREVALENCE IN PIACENZA AND IN RELATION TO THE DISTRICT OF ORIGIN

The only District where the prevalence is in accordance with the expectations of “traditional” data, both national and international, is the Eastern one. The Western District, the smallest of the three, results having more than twice the patients diagnosed with ALS during the period of observation (01/01/2019 – 01/06/2019) with Prevalence values three times the first one. The Urban District shows a Prevalence similar to the Western one with a population almost as numerous as the major District (see table n°10 PREVALENCE PER LOCAL HEALTH CARE UNIT DISTRICTS OF PIACENZA)
We decided to recalculate the Prevalence taking into account only the population of same age as patients.

In our specific environment, actually, during the 15-year duration of this study we have never had patients younger than 40.

It is clear that the values, already relevant if compared to the general population, become even more relevant – in the same District proportion as already seen in the previous table – counting almost 30 cases every 100,000 residents in the City and Western Districts. The average in the province too is over 20 patients diagnosed with ALS every 100,000 same age residents.

(see table n°11 PREVALENCE PER DISTRICT VS THE SAME AGE POPULATION (same age: >40)).

**PREVALENCE RELATED TO PATIENT ORIGIN PER ALTITUDE ZONE**

Since, as already mentioned here above, the distribution per Districts responds to a merely administrative logic, we deemed it could be of interest to calculate the Prevalence from a more strictly environmental point of observation, therefore with greater connection to people's life-style and natural history, i.e. from a perspective referred to the distribution of patients based on their being resident in the Mountain municipalities (high Apennines), in the countryside (plain/hill), or rather more urbanized although not more densely populated (province capital). Furthermore, in the timeframe between 01/01/2019 and 01/06/2019, the patients have been in-charge for different periods of time. (See table n° 12 HISTORIC PHASE OF PATIENT TAKING CHARGE PER ALTITUDE ZONE IN 2019): 3 of the 39 patients in charge from 01/01/2019 and 01/06/2019 have been in charge for over 10 years (1st Block), 9 of them for a period ranging from 10 to 6 years, while 27 - equally distributed between countryside and city, with an extremely low presence of mountain residents - have been taken over during the latest 5 years.

The Prevalence calculated based on the distribution on the natural territory - both on the overall province l and in the mountain, plain and hill territories - (table no. 8), results in line with the expected values as per EURALS Consortium, in other words and as already seen, double than usually illustrated in literature [22].

Only the value relative to the urban area, with over 17 cases per 100,000 residents, is sensibly higher also compared to the new Prevalence indexes. As well as in the case of the distribution per districts, we have calculated the Prevalence vs same age residents also based on their natural distribution (see table n°13 PREVALENCE PER ALTITUDE ZONE 2019).

Of course, also in this case the Prevalence values are higher - even if in a less relevant way compared to the distribution per Districts - than the percentage calculated on general population. Once again, it is the city that shows the most significant values with 7 cases more than the provincial average and indeed 10 cases more than the mountain and country municipalities. (see table n°14 PREVALENCE PER ALTITUDE ZONE (2019) VS SAME AGE).

**PREVALENCE RELATED TO PATIENTS’ AGE RANGE**

one third of the patients in the timeframe between 01/01/2019 and 01/06/2019, have been being in charge for a period ranging from 16 and 6 years (12/39 –30,76%). Among them, almost 60% were younger than 65 at the time they were diagnosed, and the others fell in the category of the so-called young-elders (65/75 years old). (see table n°15 HISTORIC PHASE OF PATIENTS TAKING CHARGE PER AGE-RANGE IN 2019).

The Prevalence rate vs the same age population indicates an age-related pattern of progressivity, with values that double in the 65/75 age range vs younger population and then remain practically stable in the over-75 age range. (see table n°16 PREVALENCE BY AGE RANGE (2019) VS SAME AGE POPULATION).

As a conclusion, the data about ALS Prevalence in the Province of Piacenza seem to show important peaks, higher than any epidemiologic standard, in particular in the urban area and among the older age population: as a matter of fact, ageing is an important factor related to the development of the disease [23]. The average age of the population resident in the Province of Piacenza is one of the highest on a national and European level. In particular, the values given in table 5 (prevalence vs same age) suggest how degenerative neuromuscular pathologies taken in charge by the DTCP of Piacenza could not be limited to clear ALS. There seem to be an important difference between the prevalence related to the urban population and that of the population resident in the country, hill and mountain, independently from the numerosness of the reference population. As already put in evidence, the progression towards a constant increase of ALS Prevalence is reported in uniform way in literature, and the reason is attributed to the improvement in palliative treatment, in the conditions of life of the sick person and to the ethic and cultural change in his life decisions and daily lifestyle [9],[14].

Other factors of incidence are, from one side and in certain cases, the generally improved diagnostic capability but, on the other side, also the opposite problem of the diagnostic accuracy – often recorded in literature – with a possibility of diagnostic errors in 5–10% of the cases [17], [24]. The restrictive effect of bias selection on the value regarding the number of diagnosis in tertiary facilities (with approx. 7% of non-confirmed diagnosis) has been evidenced even recently. This means that the number of diagnosis counted in epidemiology may be actually lower that the real one [25]. On the contrary, in our study we did not use any case selection and categorization mode, which means that all cases
have been counted in the same way, based on their entering the DTCP, without differentiating the counting mode according to El Escorial's Criteria1. [13],[19].

**Incidence**

Even the rate of new diagnosed ALS cases per year in Italy reported in literature is variable, depending on the sources, from 1,5 and 4 every 100.000 residents. The indicated values are 1,5 – 2 cases every 100.000 residents per year [17] with approx. 1,000 new diagnosis/year in Italy. According to the DTCP report of AISLA (the Italian ALS Association) issued in 2017, the values in Western Europe are 2,35 new cases/100.000 residents, and in Italy 283 cases every 100.000 residents (the incidence in Emilia Romagna is of 2,64 cases every 100.000 residents)[20]. According to other sources, ALS has an incidence of 1,2–4,0 cases every 100.000 persons/year [26]. According to the population-based records the incidence of sporadic amyotrophic lateral sclerosis (SALS) in Europe – including Italy – and in North America is certified at 1,7 – 2,3 cases each 100.000 persons/year (average 1,89 every 100.000 persons/year). "In order to reach more reliable incidence rates and make the results clear and comparable, it is necessary to use standard classification criteria on great dimension populations. In recent years, studies have been conducted on significant populations through national and regional registries and, based on El Escorial's criteria the incidence of ALS resulted to be quite stable, ranging between 1,7 and 2,5 cases every 100.000 persons/year"[17]. Same as for Prevalence, also for the Incidence rate, in February 2020 AISLAs website reports – based on the data supplied by EURALS Consortium (the European consortium of Amyotrophic Lateral Sclerosis) updated as at February 2020 – values of 3–4 every 100.000 residents, with an incidence, in Italy, of 2000 new cases/year [22].

- The previous considerations about Prevalence are generally valid also for the Incidence Rate, with an incidence in rural areas in 2018 of 2,78/100.000 and in the urban district of 7,76/100.000, in 2017 of 3,83/100.000 and in 2016 of 3,48/100.000, but in the west district of 6,50/100.000. (see table n° 17,18,19 **ALS INCIDENCE IN THE PROVINCE OF PIACENZA CALCULATED PER YEAR DURING THE LAST THREE YEARS** (2018–2017 – 2016)

Besides, if the little dimensions of the segments of the reference population may cause value distortion effects (e.g. for the Western District), in any case the ALS Incidence Rate in the province shows a stable trend and falls into the high range of expected national and international values. It is instead evident that the trend of the Incidence Rate in the urban area is higher than both the provincial and national ones. (SEE TABLE N°20 **AVERAGE ALS INCIDENCE RATE IN THE PROVINCE OF PIACENZA CALCULATED ON THE LAST THREE YEARS**).

**Conclusions**

The formalization of the DTCP changed the clinic demographic cohort over time, showing an increase in number of patients took in charge, with even more advanced ages, with harder symptomatologies to detect. The clinical focus has been moved to the urban district, allowing the hypotization of an environmental influence on the disease genesis as shown in literature [27],[28],[29]. The detected prevalence is much higher of the national and international mean found in literature, while the incidence is stable, with the same expected values.

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### Tables

**TABLE No.1 STAGING CRITERIA**

| STAGE 1 | STAGE 2 | STAGE 3 |
|---------|---------|---------|
| B       | M       | C       |
| Score ≥2 in max. two areas | Score ≥2 in at least three areas | Score 4 in the B area |

**Breathing B**

1. Normal
2. Mild restrictive insufficiency (70%<CV<80%)
3. Restrictive insuiciency with night NIV indication (50%<CV<70%)
4. Need of day and night NIV (12-18 hrs)
5. NIV/tracheostomy with complete dependence on mechanical ventilation (24 hrs)

Mobility
1. Normal
2. Impaired mobility that do not interfere with the lifestyle
3. Impaired mobility that interfere with the lifestyle but without compromise of autonomy (no wheelchair)
4. Impaired mobility that compromise autonomy with no need of continuous care
5. Severe disability and total dependence on continuous care

Nutrition N
1. Natural nutrition
2. Nutrition that requires nutritional advice (modification of diet consistency only)
3. Nutrition that requires nutritional supplement
4. Artificial nutrition (PEG nutrition or parenteral nutrition for patients refusing PEG)

Communication C
1. Normal
2. Dysarthria but intelligible speech
3. Anarthria with ability to use simple communicators
4. Anarthria with ability to use high-tech communicators
5. Anarthria with no ability to use high-tech communicators

DEMOGRAPHY

TABLE No.2 NUMBER OF PATIENTS

| NUMBER OF PATIENTS | 1st BLOCK (2004-2009) | 2nd BLOCK (2010-2014) | 3rd BLOCK (2015-2019) | TOTAL |
|--------------------|------------------------|------------------------|------------------------|-------|
| Average age (in years) | 20 | 52 | 48 | 120 |
| Max | 65 | 80 | 74 | 70 |
| Min | 47 | 46 | 42 | 42 |
| SD | 6 | 11 | 11 | 11 |

TABLE No.3 PATIENTS BY AGE GROUP (ABSOLUTE VALUE AND PERCENTAGE)

| BLOCK 1 (04/09) | BLOCK 2 (10/14) | BLOCK 3 (15/19) | TOTAL |
|-----------------|-----------------|-----------------|-------|
| < 65 years | 8\20 | 40% | 15\52 | 29% | 12\48 | 25% | 33\120 | 27,5% |
| 65-75 years | 11\20 | 55% | 22\52 | 42% | 8\148 | 16,7% | 43\120 | 35,8% |
| > 75 years | 1\20 | 5% | 15\52 | 29% | 28\48 | 58,3% | 44\120 | 36,7% |

TABLE No.4 PATIENTS PER GENDER

| GENDER | BLOCK 1 (04/09) | BLOCK 2 (10/14) | BLOCK 3 (15/19) | TOTAL |
|--------|-----------------|-----------------|-----------------|-------|
| MALE | 10 | 25 | 23 | 58 |
| FEMALE | 10 | 27 | 25 | 62 |

TABLE No.5 ORIGIN OF PATIENTS IN ABSOLUTE VALUE

| ORIGIN OF PATIENTS | BLOCK 1 (04/09) | BLOCK 2 (10/14) | BLOCK 3 (15/19) | TOTAL | RESIDENTS (same age 40\95) |
|-------------------|-----------------|-----------------|-----------------|-------|-------------------------|
| WESTERN           | 5 | 15 | 10 | 30 | 47898 |
| CITY              | 8 | 25 | 20 | 53 | 62487 |
| EASTERN           | 7 | 12 | 15 | 34 | 67068 |
| NON-HCU           | 3 | 3 | 3 | 3 | 9 |
| PROVINCE          | 20 | 52 | 48 | 120 | 177453 |
**TABLE No.6 ORIGIN OF PATIENTS IN PERCENTAGE**

| BLOCK     | 1st BLOCK (0409) | 2nd BLOCK (1014) | 3rd BLOCK (1519) | TOTAL |
|-----------|------------------|------------------|------------------|-------|
| WESTERN   | 35,00%           | 23,00%           | 20,80%           | 25,00%|
| CITY      | 40,00%           | 48,00%           | 41,70%           | 44,20%|
| EASTERN   | 25,00%           | 29,00%           | 31,25%           | 28,30%|
| NON-HCU   |                  |                  |                  | 6,25% |
| PERCENTAGE (%) OF TOTAL NUMBER OF PATIENTS | 16,70% | 43,30% | 40,00% | 100,00% |

**TABLE No.7 ORIGIN BY ALTITUDE ZONE IN ABSOLUTE VALUE (TOTALITY OF PATIENTS)**

*MINUS NON-HCU PATIENTS  **Italian National Statistical Institute

| ORIGIN OF PATIENTS BY ISTAT** ALTITUDE ZONE (V.A.) - ABSOLUTE NUMBERS | RESIDENT POPULATION (same age) - ABSOLUTE NUMBERS |
|-----------------------------------------------------------------------|--------------------------------------------------|
| <65 | 65/75 | >75 | TOTAL | 40/65 | 65/75 | 75/95 |
| Mountain municipalities | 4 | 4 | 1 | 9 | 5,290 | 2,326 | 3,265 |
| Hill- and plain-area municipalities | 15 | 19 | 23 | 57 | 64,474 | 18,569 | 21,042 |
| City | 13 | 20 | 18 | 51 | 37,550 | 11,194 | 13,743 |
| WHOLE PROVINCE* | 32 | 43 | 42 | 117 | 107,314 | 32,089 | 38,050 |

**TABLE No.8 ORIGIN BY ALTITUDE ZONE IN PERCENTAGE (TOTALITY OF PATIENTS)**

**Italian National Statistical Institute

| ORIGIN OF PATIENTS BY ISTAT** ALTITUDE ZONE (%) | RESIDENT POPULATION (same age) (%) |
|------------------------------------------------|-----------------------------------|
| <65 | 65/75 | >75 | TOTAL | 40/65 | 65/75 | 75/95 |
| Mountain municipalities | 12,50 | 9,30 | 2,20 | 7,50 | 4,95 | 7,24 | 8,58 |
| Hill- and plain-area municipalities | 47,00 | 44,20 | 51,10 | 47,50 | 60,00 | 57,86 | 55,30 |
| City | 40,50 | 46,50 | 40,00 | 42,50 | 34,95 | 34,88 | 36,11 |
| Non-HCU | 6,70 | 2,50 | 4 | 0 | 0 | 0 | 0 |

**TABLE No.9 ORIGIN OF PATIENTS BY ALTITUDE ZONE GROUPED BY TIMEFRAME IN ABSOLUTE VALUES**

| BLOCK 1 (2004-2009) | MOUNTAIN | PLAIN | CITY | TOTAL |
|----------------------|----------|-------|------|-------|
| TOTAL                | 4        | 8     | 8    | 20    |
| <65                  | 2        | 4     | 2    | 8     |
| 65/75                | 2        | 4     | 5    | 11    |
| >75                  | 0        | 0     | 1    | 1     |
| BLOCK 2 (2010-2014) | MOUNTAIN | PLAIN | CITY | TOTAL |
| TOTAL                | 3        | 26    | 23   | 52    |
| <65                  | 1        | 6     | 7    | 14    |
| 65/75                | 2        | 11    | 10   | 23    |
| >75                  | 0        | 9     | 6    | 15    |
| BLOCK 3 (2015-2019) | MOUNTAIN | PLAIN | CITY | TOTAL |
| TOTAL                | 2        | 23    | 20   | 45*   |
| <65                  | 1        | 5     | 4    | 10    |
| 65/75                | 0        | 4     | 5    | 9     |
| >75                  | 1        | 14    | 11   | 26    |

*NON-HCU PATIENTS NOT CONSIDERED

**PREVALENCE**

**TABLE No.10 PREVALENCE PER LOCAL HEALTH CARE UNIT DISTRICTS OF Piacenza**

| PREVALENCE PER DISTRICT | PATIENTS IN CHARGE IN 2019 | RESIDENT POPULATION (TOTAL) | PT/100.000 RES. | PERCENTAGE ON POPULATION |
|-------------------------|----------------------------|----------------------------|-----------------|--------------------------|
| WESTERN                 | 14                         | 76.810                     | 18.22/100.000   | 0.018%                   |
| CITY                    | 18                         | 103.942                    | 17.31/100.000   | 0.017%                   |
| EASTERN                 | 7                          | 106.400                    | 6.57/100.000    | 0.006%                   |
| WHOLE PROVINCE          | 39                         | 287.152                    | 13.58/100.000   | 0.013%                   |
| Non-HCU                 | 4                          |                            |                 |                          |
TABLE No.11 PREVALENCE PER DISTRICT VS THE SAME AGE POPULATION (same age: >40)

| DISTRICT       | PATIENTS IN CHARGE IN 2019 | RESIDENT SAME AGE POPULATION | PT/100.000 SAME AGE RES. | PERCENTAGE ON SAME AGE POPULATION |
|----------------|-----------------------------|------------------------------|--------------------------|-----------------------------------|
| WESTERN        | 14                          | 48.168                       | 29.06/100.000            | 0.029%                            |
| CITY           | 18                          | 62.896                       | 28.61/100.000            | 0.028%                            |
| EASTERN        | 7                           | 67.489                       | 10.37/100.000            | 0.010%                            |
| WHOLE PROVINCE | 39                          | 178.553                      | 21.84/100.000            | 0.021%                            |
| Non-HCU        | 4                           |                              |                          |                                    |

TABLE No.12 HISTORIC PHASE OF PATIENT TAKING CHARGE PER ALTITUDE ZONE IN 2019

| HISTORIC PHASE - pt in charge from: | MOUNTAIN | PLAIN/HILL | CITY | TOTAL 2019 |
|------------------------------------|----------|------------|------|------------|
| 2004 – 2009 - 1st BLOCK            | 0        | 1          | 2    | 3          |
| 2010 – 2014 - 2nd BLOCK            | 1        | 4          | 4    | 9          |
| 2015 – 2019 (June) – 3rd BLOCK     | 1        | 14         | 12   | 27         |
|                                    | 2        | 19         | 18   | 39         |

TABLE No.13 PREVALENCE PER ALTITUDE ZONE (2019)

| Altitude Zones | PATIENTS | RESIDENT POPULATION (TOTAL) | PREVALENCE | PERCENTAGE |
|----------------|----------|------------------------------|------------|------------|
| MOUNTAIN       | 2        | 14.744                       | 13.52/100.000 AB | 0.013%    |
| PLAIN/HILL     | 19       | 168.466                      | 11.27/100.000 AB | 0.011%    |
| CITY           | 16       | 108.942                      | 17.31/100.000 AB | 0.017%    |
| WHOLE PROVINCE | 39       | 287.152                      | 13.58/100.000 AB | 0.013%    |

TABLE No.14 PREVALENCE PER ALTITUDE ZONE (2019) VS SAME AGE

| Altitude Zones | PATIENTS | RESIDENT POPULATION (same-age: > 40) | PT/100.000 RES. SAME AGE RESIDENTS | PERCENTAGE ON SAME AGE POPULATION |
|----------------|----------|--------------------------------------|-----------------------------------|-----------------------------------|
| MOUNTAIN       | 2        | 11.008                               | 18.16/100.000 AB                  | 0.018%                            |
| PLAIN/HILL     | 19       | 104.649                             | 18.15/100.000 AB                  | 0.018%                            |
| CITY           | 18       | 62.896                               | 28.61/100.000 AB                  | 0.028%                            |
| WHOLE PROVINCE | 39       | 178.553                             | 21.84/100.000 AB                  | 0.021%                            |

TABLE No.15 HISTORIC PHASE OF PATIENTS TAKING CHARGE PER AGE-RANGE IN 2019

| HISTORIC PHASE - pt in charge from: | 40\65 | 65\75 | >75 | TOTAL 2019 |
|------------------------------------|-------|-------|-----|------------|
| 2004 – 2009 - 1st BLOCK            | 3     | 0     | 0   | 3          |
| 2010 – 2014 - 2nd BLOCK            | 4     | 5     | 0   | 9          |
| 2015 – 2019 (June) – 3rd BLOCK     | 9     | 5     | 13  | 27         |
|                                    | 16    | 10    | 13  | 39         |

TABLE No.16 PREVALENCE BY AGE RANGE (2019) VS. SAME AGE POPULATION

| AGE RANGE | PATIENTS | RESIDENT POPULATION (same age) | PT/100.000 SAME AGE RESIDENTS | PERCENTAGE ON SAME AGE POPULATION |
|-----------|----------|-------------------------------|-------------------------------|-----------------------------------|
| 40\65     | 16       | 107.314                       | 14.90/100.000 AB              | 0.014%                            |
| 65\75     | 10       | 32.089                        | 31.16/100.000 AB              | 0.031%                            |
| >75        | 13       | 39.150                        | 33.20/100.000 AB              | 0.033%                            |
| WHOLE PROVINCE | 39     | 178.553                       | 21.84/100.000 AB              | 0.021%                            |

INCIDENCE

TABLE No. 17 ALS INCIDENCE IN THE PROVINCE OF PIACENZA CALCULATED PER YEAR DURING THE LAST THREE YEARS (2018 – 2017 – 2016)
| Year | Resident Population | New Cases | Incidence Rate |
|------|---------------------|-----------|----------------|
| 2018 | Whole Province      | 287,152   | 10 (8)         |
|      | West                | 76,810    | 0              |
|      | City                | 103,083   | 8              |
|      | East                | 107,259   | 0              |
|      | Non-HCU             | 2         |
|      | **INCIDENCE 2018**  | **2,78/100.000 AB** |

| Year | Resident Population | New Cases | Incidence Rate |
|------|---------------------|-----------|----------------|
| 2017 | Whole Province      | 286,781   | 11             |
|      | West                | 76,951    | 3              |
|      | City                | 103,082   | 5              |
|      | East                | 106,748   | 3              |
|      | Non-HCU             | 1         |
|      | **INCIDENCE 2017**  | **3,83/100.000 AB** |

| Year | Resident Population | New Cases | Incidence Rate |
|------|---------------------|-----------|----------------|
| 2016 | Whole Province      | 286,758   | 11 (10)        |
|      | West                | 76,887    | 5              |
|      | City                | 102,355   | 3              |
|      | East                | 107,516   | 2              |
|      | Non-HCU             | 1         |
|      | **INCIDENCE 2016**  | **3,48/100.000 AB** |

**TABLE No.18**

**TABLE No.19**

**TABLE No. 20 AVERAGE ALS INCIDENCE RATE IN THE PROVINCE OF PIACENZA CALCULATED ON THE LAST THREE YEARS**

| Region  | Incidence Rate |
|---------|----------------|
| Total Province | 3,36/100.000 AB |
| West    | 3,46/100.000 AB |
| City    | 5,18/100.000 AB |
| East    | 1,55/100.000 AB |